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THE DILUTION CURVE OF ACTIVITY IN ARTERIAL BLOOD AFTER INTRAVENOUS INJECTION OF LABELED CORPUSCLES

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THE prolongation of the circulation time, determined by the decholin method in heart insufficiency, is not only an expression of the degree of stasis but also of the dilatation of the heart and thus of the residual blood in the heart.[1-4] In compensated cardiological cases there is a clear connection between the circulation time and the roentgenologic volume of the heart.[3] In other words the greater the heart volume the longer its circulation time, a circumstance which is further illustrated by a more detailed statistical investigation of a large amount of material.[5] It has also been possible to prove static, simultaneous changes in the amount of residual blood in the heart and in the circulation time.[3] The connection, not previously observed, between the length of the circulation time and the amount of the residual blood in the heart explains observations made earlier, *inter alia*, by Weiss[6] and Nylin and co-workers. In certain cases of heart insufficiency there was little or no change, i.e., shortening, in the circulation time in spite of the symptoms of insufficiency, and the stasis phenomenon yielded to therapy, which is explained by the fact that the dilatation of the heart persisted.

The circulation time is thus extremely dependent on the mixing conditions of the injected test substance in the heart cavities. I have shown earlier that, with the decholin method, not only the first taste sensation but at times also the duration of the sensation is an expression of the amount of the residual blood. In several respects, however, the decholin method is not satisfactory. A more detailed analysis of the afore-mentioned circulation phenomenon presupposes that a test substance which remains constantly attached preferably to the red blood corpuscles for a relatively long space of time can be introduced into the circulating blood and subsequently analyzed with satisfactory exactness on blood specimens. The test substances which have been employed in recent times, such as certain dye substances, vital red and, above all, "Evans Blue" T-1824, carbon monoxide, and certain other substances, such as decholin, histamine, saccharin, and lobeline lack, more or less, these afore-mentioned prerequisites. By the method of Hevesy and his co-workers,[7-9] i.e., labelling the red blood corpuscles with radioactive isotopes, in the first place 32 P, a

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new field was opened up for circulation research. In a preliminary work Nylin and Malm[10] showed that this method of labelling and subsequent analysis is applicable to investigations into the mixing conditions in cases of different amounts of residual blood in the heart. Hevesy and others[11] have applied the method for determining the circulating blood volume in healthy persons, and they discuss in detail the sources of error from which this method may conceivably suffer. How uniformly the radioactive phosphorus is attached to the red blood corpuscles appears to be of the greatest significance. From the investigations of Hevesy and his co-workers it seems to emerge that the chances of radioactive phosphorus infiltrating into the blood corpuscles from the radioactive plasma are many times greater than those of radioactive phosphorus being expelled from the blood corpuscles into the plasma, but on the other hand that the resorption from the plasma of the radioactive phosphorus through the capillary wall is extremely rapid. Even if allowance is made for the error of the method, due to some active plasma being left with the decentrifuged red blood corpuscles, when the activity of the different specimens is determined, the total error ten minutes after the injection appears to amount to only 0.5 per cent. From my investigations it appears that relatively constant values of the activity are still obtained twenty minutes after the injection of the labelled blood corpuscles.

From what has been said it emerges that Hevesy's method affords possibilities of studying certain circulation phenomena with greater exactness than earlier methods afforded and satisfies the prerequisites for analyzing more closely the connection between the magnitude of the residual blood in the heart and the circulation time. It appeared that the decholin times were correlated with the type of the dilution curve of the activity in the arterial blood.

For the purpose of studying more thoroughly and of throwing light upon the afore-mentioned observations, the investigations were extended to comprise both normal cases and certain cardiological cases.

METHOD

On the whole, the procedure described in the first published work was followed.[10] As a rule we took 6 c.c. of blood from the patient in the morning by means of venous puncture. This was put into a paraffined flask containing approximately 0.3m C radioactive phosphorus. The flask was then shaken in a thermostat at 37° C. for two hours. Half the labeled blood, i.e., 3 c.c., was then injected into a vein in one of the patient's arms. The injecting was carried out rapidly during the course of one to two seconds. The patient lay in a horizontal position and quite still during the experiment. Before the injection of the labeled blood corpuscles, a puncture of the arteria brachialis of the other arm was made, and a specimen-taking cannula, fitted with a tap, was inserted.

Fractioned specimens were then taken and collected in small glass tubes immediately after the intravenous injection of the labeled blood corpuscles. The times of the specimen taking (as shown by stop watches) are accurately given in seconds after the injection. The remainder of the labeled blood corpuscles which were not injected and the various fractioned specimens were dealt with in the manner described in an earlier work, and finally the activity was determined for each specimen with the Geiger counter. First, the activity is

given by the number of impulses per gram of blood corpuscles, i. e., the specific activity, and second, the activity of the different specimens is expressed as a percentage of the most strongly labeled specimen, i.e., the relative activity. Further, for all the healthy experimental persons and for the patients, measurements were made of the venous pressure. The circulation time was determined by the decholin method, and the roentgenologic heart volume was determined. In determinations of the heart volume the method which has previously been published was employed.[12]

RESULTS

The material comprised five experimental persons who were healthy from the point of view of circulation, and six persons with heart disease, the latter consisting of five without signs of heart decompensation, and finally, one with typical heart insufficiency and cardiosclerosis. This patient had been followed with repeated circulation investigations over a long period, until, after appropriate therapy, all signs of insufficiency had disappeared. The five compensated heart cases comprised one instance of aortic insufficiency (Case 6), an instance of combined mitral stenosis and aortic insufficiency (Case 7), an instance of cardiosclerosis (Case 8), an instance of hypertonia (Case 9), and, finally, an instance (Case 10) of operated concretio cordis. A survey of all the cases is given in Table I, containing the most important data as to the heart volumes, circulation times, and venous pressures.

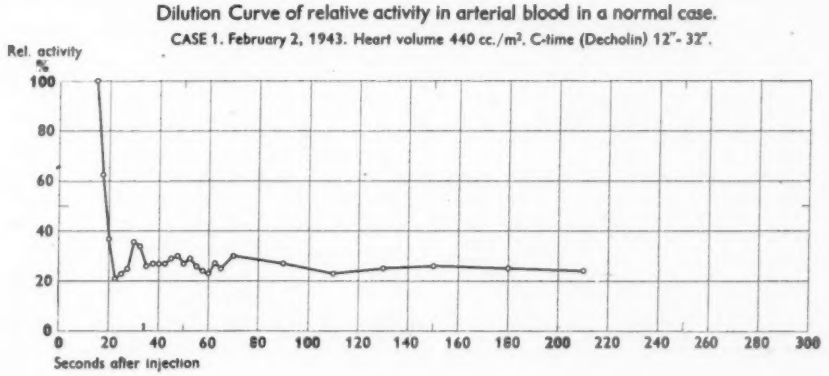

Fig. 1.

The material is not large, but owing to the considerable number of the fractioned specimens—in each case between 30 and 40—and the time-consuming method of ashing the specimens, it has not yet been possible to investigate a larger number.

It appears from Table I that all the heart volumes in the healthy persons were within normal limits. The upper limit for the normal, according to what has been indicated earlier, is 500 c.c./m² of body surface. The circulation times determined with decholin are short and within normal limits. Thus, on an average, the first taste sensation was perceived after fourteen seconds, and the bitter taste disappeared after thirty-two seconds. The first figure agrees with the mean value of twelve seconds observed on a considerable normal material in an earlier work. The means figure for the cessation of the taste sensation is higher than the corresponding figure of twenty-five seconds in the last-mentioned work.

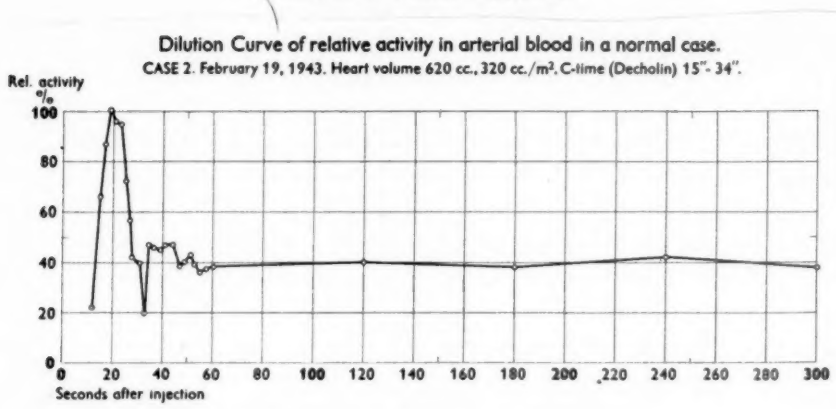

Fig. 2.

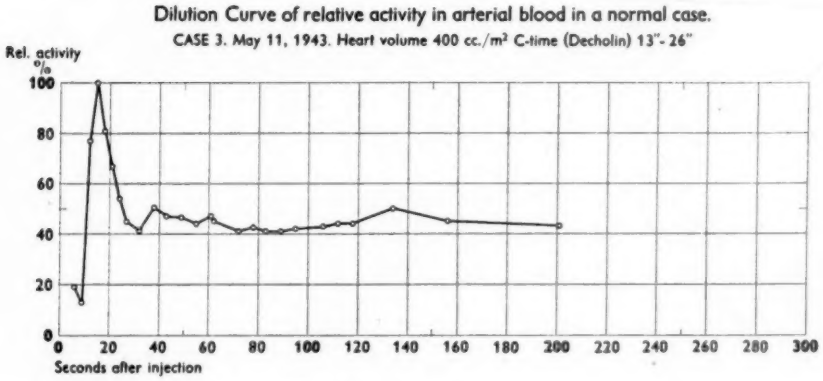

Fig. 3.

TABLE I

	CASE	DATE	DIAGNOSIS	VENOUS PRESSURE (CM.)	HEART VOLUME (C.C.)	HEART VOLUME (C.C./M²)	CIRCULATION TIME (DECHOLIN) (SEC.) FIRST SENSATION	CIRCULATION TIME (DECHOLIN) (SEC.) LAST SENSATION
Normal cases	1	Feb. 9, 1943				440	12	32
	2	Feb. 19, 1943			620	320	15	34
	3	May 11, 1943				400	13	26
	4	Oct. 11, 1942			880	450	12	25
	5	Feb. 8, 1944			978	500	17	42
Mean						422	14	32
Compensated heart cases	6	March 30, 1943	Aortic regurgitation?	13	1480	750	14	30
	6	May 25, 1943	Aortic regurgitation?	14	1470	785	16	30
	7	June 9, 1943	Mitral stenosis and aortic regurgitation	11	1460	820	17	30
	7	(July 14, 1943)	Mitral stenosis and aortic regurgitation	(8)	1680	970	22	65
	8	June 22, 1943	Cardiosclerosis	5	(1470)	(860)	(20)	(45)
	9	March 16, 1944	Hypertension	13	1480	830	32	83
	10	June 12, 1944	Constrictive pericarditis	10	2100	1200	37	85
					820	470	13	29
Mean						851	24	59
Decompensated heart cases	11	May 15, 1944	Cardiosclerosis	17	1610	895	35	65
	11	May 25, 1944	Cardiosclerosis (compensated)	5	1350	845	21	44

The dilution curves for the relative activity in the arterial blood in the normal cases is shown in the diagrams, Figs. 1, 2, 3, 4, and 5. From these it appears that there is good agreement between, first, the different normal cases, and second, the dilution curves for the radioactive labeling and the decholin times. Equilibrium appear fairly rapidly, as is shown in the diagram, sometimes after about sixty seconds and, as a rule, during the second minute after the intravenous injection. Similarly it appears that the activity remains strikingly constant during the following four minutes, and in one normal person (Case 5) it remained relatively constant up to fifteen minutes after the injection, as is shown by Fig. 5. In another case, simultaneously fractioned specimens were taken from both arterial and venous blood, beginning at the second minute after the injection of the labeled blood corpuscles. In Table II will be

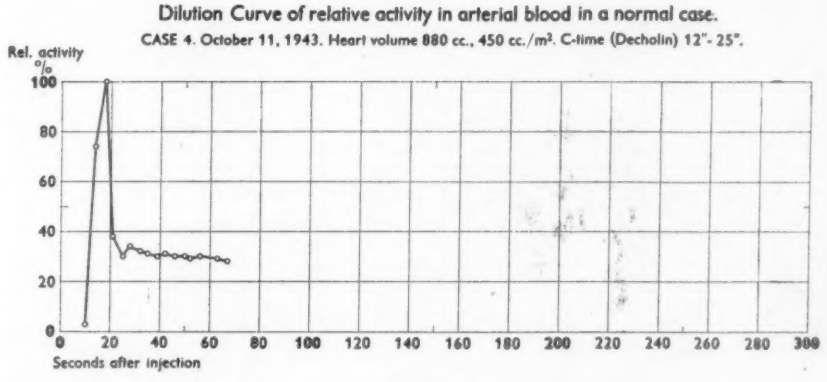

Fig. 4.

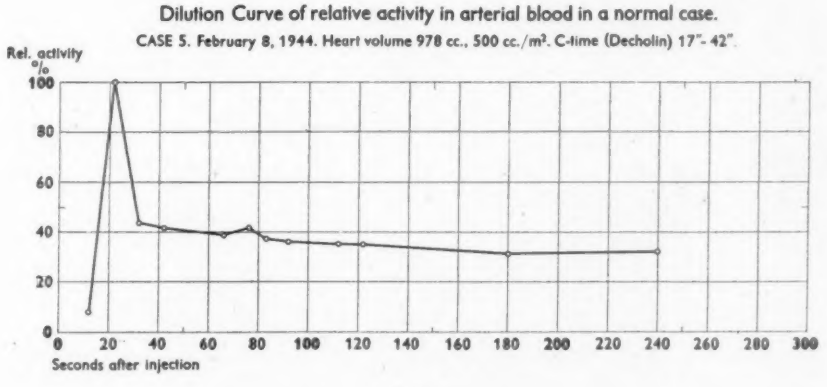

Fig. 5.

found the values for the specific activity, which prove to be relatively constant from the second up to and including the twenty-first minute after the injection. There is remarkable agreement between the values of the arterial and venous specimens. It is very important to know more exactly how long the activity remains constant in the blood and to study more in detail the decrease in activity some considerable time after the injection. In one case the specific activity in the venous blood was determined several days in succession, and this gave the result that after 48 hours the specific activity of the red blood corpuscles had fallen by 44 per cent, after 72 hours by 60 per cent, after 144 hours by 85 per cent, and after 168 hours by 93 per cent of the equilibrium value.

As has been mentioned previously and as emerges from the tables, the pathologic heart cases comprised five compensated cases and one typical case of heart decompensation. The heart volumes in the compensated cases are very large as a rule, with the exception of one case of concretio cordis which was freed by an operation from its chronic heart tamponade. The mean value of the five heart volumes amounts to 851 c.c./m^2 of body surface, i.e., double the value for that of the normal heart cases. On an average, the circulation times determined with decholin were, for the first taste sensation, 24 seconds, and for the last taste sensation, 59 seconds. Thus, in spite of the absence of stasis the

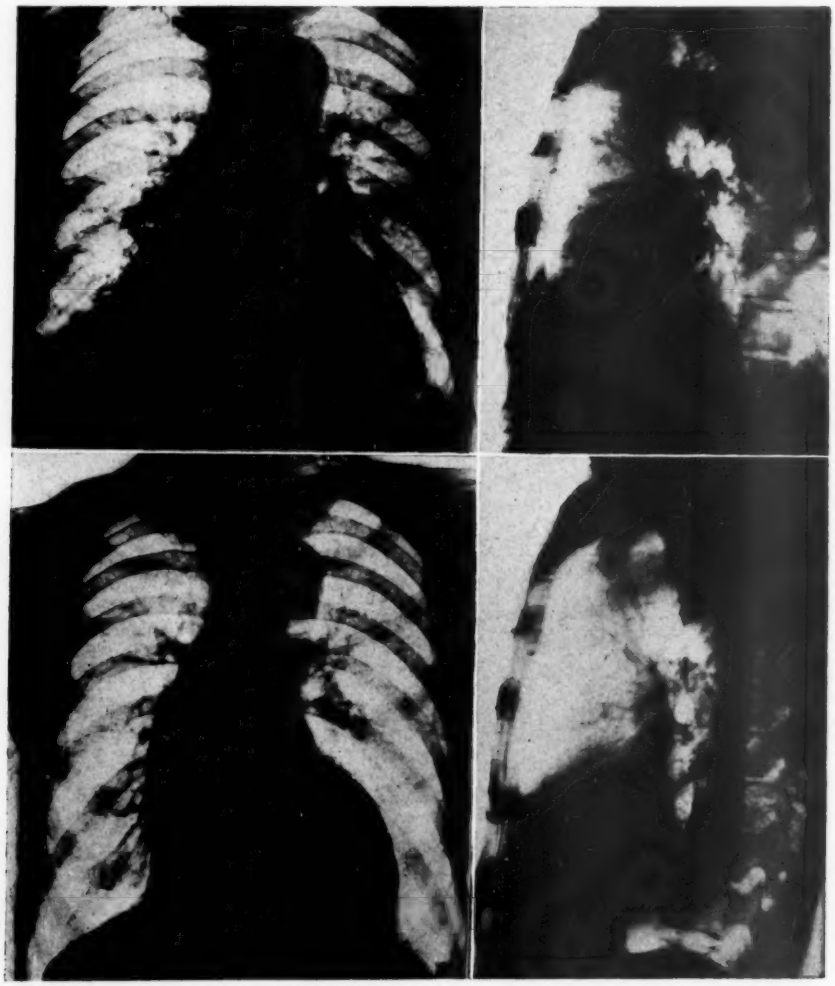

Fig. 6.—Case 11. Decompensated cardiosclerosis. After treatment, heart volume decreased 260 cubic centimeters.

circulation times are nearly twice the normal. Case 10, with a normal-sized heart, exhibits normal circulation times. Entirely contrary to my experience, i.e., that long circulation times are met with in cases of heart dilatation and large amounts of residual blood, Case 6 exhibited remarkably short and completely normal circulation times after repeated controls, an interesting circumstance which will be discussed more in detail later. Finally, on admission to the clinic, the last case, Case 11, showed the typical picture of grave heart decompensation in a 61-year-old man with cardiosclerosis. He exhibited diffuse

TABLE II

TIME AFTER INJECTION (MIN.)	SPECIFIC ACTIVITY (IMPULSES PER GRAM PER MINUTE)	
	ARTERIAL BLOOD	VENOUS BLOOD
2	161	
6	159	159
8	162	162
14	149	155
17	150	150
19	150	159
21	159	159
Mean	155	157

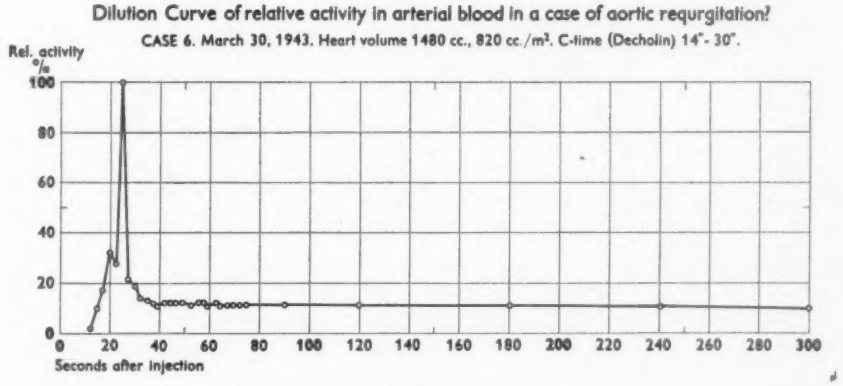

Fig. 7.

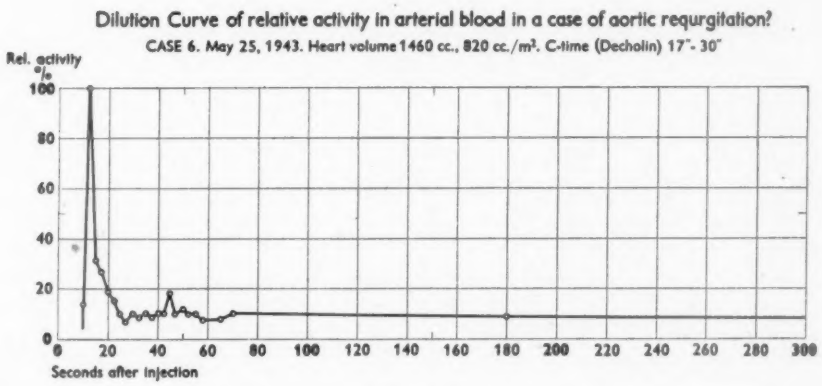

Fig. 8.

edema over the legs, thighs, and up across the back; the liver was palpated a a handbreadth below the costal margin, and, on the day of admission, the venous pressure reached a very high value, 25 centimeters. Some days later, on May 15 (see Table I), when the special examinations were made, it had fallen to 17 centimeters. The heart was strongly dilated and the heart volume greatly enlarged, namely 895 c.c./m² of body surface. The circulation times were markedly long, 35 and 65 seconds, respectively. After treatment with digitalis and diuretics, all the stasis phenomena and the edema disappeared, resulting in a decrease in weight of 10 kilograms. At the same time the circulation times were certainly shortened to 21 and 44 seconds, respectively, for the first and last taste sensations, but did not quite return to normal values. Simultaneously with the decrease in the circulation times the heart volume decreased very considerably, by nearly 300 cubic centimeters. The roentgenologic decrease in volume appears in Fig. 6.

TABLE III

TIME AFTER INJECTION (DAYS)	DECREASE IN ACTIVITY AS PERCENTAGE OF MIXING VALUE
2	44
3	60
6	85
7	93

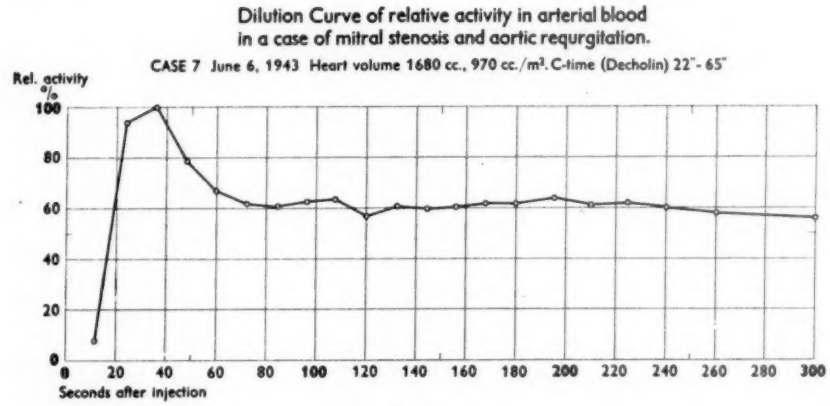

Fig. 9.

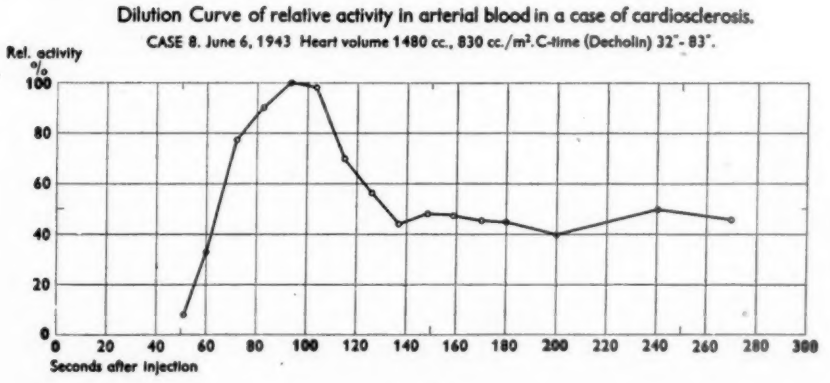

Fig. 10.

Figs. 7, 8, 9, 10, 11, 12, 13, and 14 are the dilution curves of the relative activity in the fractioned specimens from arterial blood after intravenous injection of labeled blood corpuscles. As we have found, the courses of these curves for the five compensated heart cases diverge greatly from those of the normal cases, with the exception of Case 6 (Figs. 7 and 8), a case of aortic insufficiency, and the operated case of concretio cordis (Case 10, Fig. 12). The latter has a normal heart volume, a normal dilution curve and normal circulation times. Cases 7, 8, and 9 (Figs. 9, 10, and 11) have large heart volumes and long circulation times measured by the decholin method, and in complete agreewith this the activity reaches the maximum successively and late, and then gradually and late reaches the state of equilibrium. As a rule it takes several minutes before equilibrium is attained. In Case 9 (Fig. 11) equilibrium does not appear to be reached before the seventh minute.

Case 6 was subjected to control determinations on a later occasion even with decholin. The two dilution curves (Figs. 7 and 8) show particularly consistent results and remarkable agreement with the curves for the normal cases

in spite of the fact that the heart volume is considerably enlarged, and there is reason to assume the presence of large amounts of residual blood. On several occasions, in complete conformity with the normal type of dilution curve, the decholin times have proved to be entirely normal. The explanation of the re-

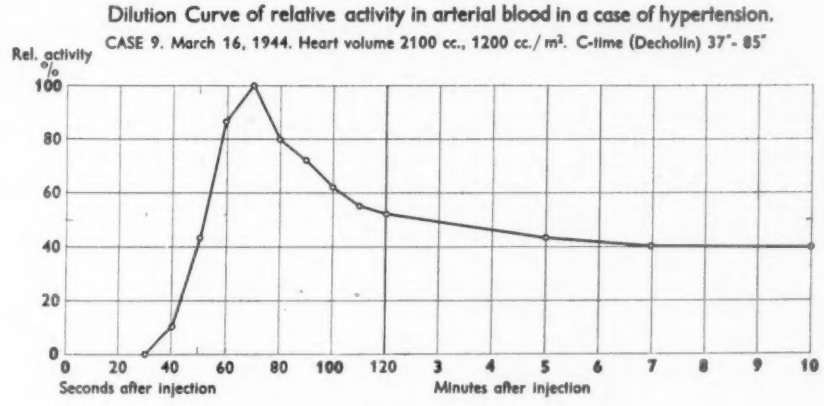

Fig. 11.

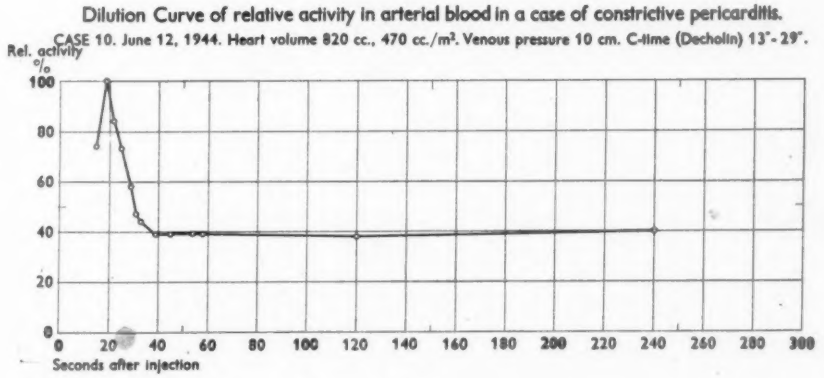

Fig. 12.

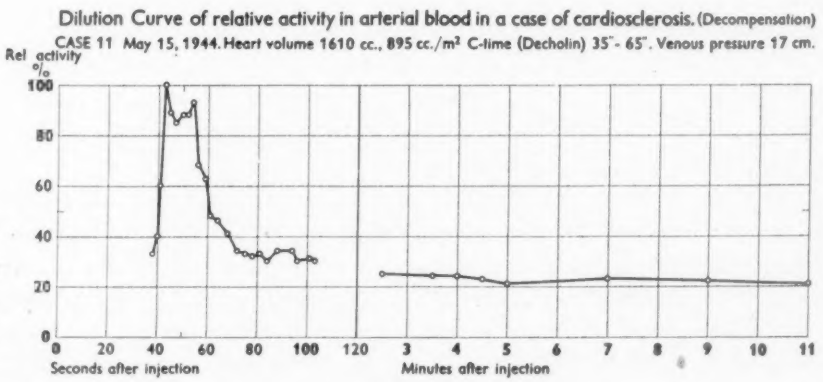

Fig. 13.

markable conditions in this exceptional case cannot be indicated with certainty. Possibly there was a defect in the ventricular septum with a dilated heart, which explains the short circulation times and the fact that the dilution curve with the radioactive labeling of the red blood corpuscles is normal.

Finally, we come to the last case, a typical heart insufficiency, which at the first examination (Fig. 13) had a high venous pressure of 17 cm., a large heart volume of 1,610 c.c., and pathologically long circulation times. Here the dilution curve is in complete agreement with those of the compensated cases with large heart volumes. Equilibrium appears late in this case, too, not before the fifth minute after the injection. Ten days later, when complete compensation had appeared, the type of curve certainly changes appreciably (Fig. 14) and to some extent approaches that of the normal cases; nevertheless the pathologic type persists. Not until the third minute is equilibrium attained. On the occasion of the last examination the circulation times also were clearly and pathologically prolonged, and at the same time the heart volume had certainly decreased but still remained considerably enlarged.

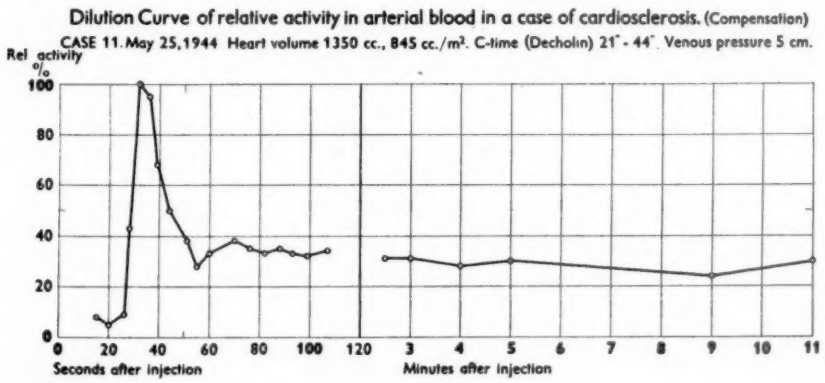

Fig. 14.

SUMMARY

Red blood corpuscles from the experimental person labeled with radioactive phosphorus were injected intravenously into the same individual, after which the activity on fractioned specimens from arterial blood was determined by means of a Geiger counter. In this way a dilution curve was obtained which appeared to be characteristic of healthy experimental persons in whom both the initial rise and the return to the position of equilibrium takes place rapidly. In pathologic heart cases with large amounts of residual blood in the heart, this dilution curve is of a completely different type, with a slow gradual rise to a maximum for the activity and subsequently a slow gradual falling part, where equilibrium is gradually reached.

There appears to be an obvious connection between the circulation times determined by the decholin method and the type of dilution curve, on the other hand and between the dilution curve and the size of the heart and the amount of the residual blood on the other. It is extremely probable that the prolonged circulation time in cases of heart insufficiency is not, as has previously been assumed, due to stasis only, but to a great extent, possibly chiefly, to the dilated heart and thus to the amount of residual blood.

For determinations of the circulating blood volume in cardiological cases it appears to be necessary to know the course of the dilution curve.

I beg to extend my warm thanks to Professor G. von Hevesy for his unfailing interest, and to Professor Manne Siegbahn, who kindly placed radioactive phosphorus at my disposal. I owe grateful thanks to Licentiate M. Malm and Professor Runnström for help with certain

of these investigations. My assistant, Miss Ingrid Larsson, has helped me indefatigably in the work, and my gratitude is also extended to the Therese and Johan Andersson Memorial Fund for a grant which made this investigation possible.

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CHANGES IN THE PRECORDIAL ELECTROCARDIOGRAM PRODUCED BY EXTENSION OF ANTEROSEPTAL MYOCARDIAL INFARCTION

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THIS report is concerned with an electrocardiographic study of two patients, each of whom experienced two attacks of severe anginal pain within a short period of time. The observations made suggest that in each case the first attack was associated with the development of a small anteroseptal myocardial infarct, whereas the second attack was related to the lateral extension of the initial lesion. The electrocardiograms illustrate the value of multiple precordial leads in the diagnosis of this sequence.

CASE REPORTS

CASE 1.—A 43-year-old housewife was admitted to the University Hospital on Aug. 6, 1943. On the morning of the day of admission to the hospital, about one hour after awakening, the patient noted mild precordial oppression which cleared spontaneously. It recurred about one hour later and became increasingly severe. Numbness in both shoulders, pain radiating to the left arm and hand, and a mild sense of suffocation developed. When examined by her physician shortly after the onset of these symptoms, the blood pressure was 160/120. Inhalation of amyl nitrite and two doses of morphine sulfate of 0.016 Gm. (¼ grain) each, subcutaneously, gave no immediate relief. She was admitted to the hospital a few hours later.

From the Department of Internal Medicine, University of Michigan Medical School. The observations reported in this article were made with the aid of a grant from the Horace H. Rackham School of Graduate Studies. They were presented in part before the Seventeenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 3, 1944.
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There was no history of previous complaints referable to the heart. The patient had been examined in the outpatient clinics on several occasions. The blood pressure was recorded as 128/100 in January, 1939, 160/110 in November, 1941, and 150/90 in March, 1942. Her father died of angina pectoris. Her mother had an abnormally high blood pressure, but died of a perforated ulcer.

Physical Examination.—When first seen, the patient was somewhat pale and drowsy. She was not complaining of pain, possibly because the opiates which had been administered at her home had become effective. The temperature, pulse rate, and respiratory rate were normal. The heart sounds were of good quality and the cardiac rhythm was normal. The blood pressure was 118/80. The remainder of the physical examination was negative.

Laboratory Data.—The blood, urine, and blood serologic examinations were negative. The leucocyte count rose from 9,300 on admission to 11,850 on the fourth hospital day, and then returned to normal. The sedimentation rate on admission was 36 mm. per hour (Wintrobe method). Subsequent determinations were 0.8 mm. per minute on September 14, 0.96 mm. per minute on September 24, and 0.4 mm. per minute on February 4, 1944 (Ernstene and Rourke method).

Clinical Course.—The usual treatment for myocardial infarction was instituted. Except for occasional palpitation, the patient was quite comfortable during the first thirty-six hours. On the evening of August 7, precordial distress recurred, and, in the early morning hours of August 8, it became quite severe, with radiation to both arms. The pain persisted with variations in intensity for thirty-six hours. During this period, four doses of morphine sulfate of 0.016 Gm. (¼ grain) each, and then five doses of dilaudid of 0.002 Gm. (1/30 grain) each, were administered. The patient grew pale, restless, and somewhat confused. She was kept in an oxygen tent for eight days. The temperature, which had been normal during the first two days, rose to 101.2° F. (R), and the pulse rate, to 116 per minute. The respiratory rate fell to 5 per minute. The blood pressure remained at about the same level as on admission. After the eighth hospital day there was progressive improvement, and convalescence was uneventful except for a mild upper respiratory infection. The patient was discharged on the fifty-second hospital day. When last seen, on Sept. 23, 1944, she was feeling well except for mild sciatica, and had been able to resume nearly full, normal activity.

Electrocardiograms.—The standard leads and unipolar extremity leads taken on August 6, six and one-half hours after the onset of symptoms, show slightly inverted T waves in Lead I and sharp terminal inversion of the T waves in Lead V_L (Fig. 1). Although somewhat suggestive, these records are not diagnostic of myocardial infarction because there are no significant changes in the QRS complexes. The precordial leads taken on August 7, twenty-seven hours after the onset of symptoms, show QS deflections in Lead V_2 and sharp terminal inversion of the T waves in Leads V_1, V_2, V_3, V_4, and V_5 (Fig. 2). These changes are characteristic of recent anteroseptal myocardial infarction. Infarcts in this location are usually not accompanied by diagnostic alterations in the standard limb leads.[1]

The standard and unipolar extremity leads on August 9 (not reproduced), thirty-six hours after the recurrence of pain, are quite different from the first electrocardiograms. Prominent Q waves, small or absent R waves, and upward displacement of the RS-T segment are seen in Leads I and V_L, together with downward RS-T displacement in Lead III. The same changes are present in the tracings taken on August 11, except that displacement of the RS-T segment is more striking (Fig. 1). The precordial leads taken on this same date show large QS deflections in Leads V_1, V_2, V_3, and V_4 and pronounced RS-T displacement in Leads V_2, V_3, V_4, and V_5 (Fig. 2). Since the cavity potential (QS deflection) is now recorded not only in Lead V_2 but from several other precordial regions, chiefly to the left of this point, it is evident that the original zone of infarction had extended laterally. The RS-T displacement also suggests that further acute injury had occurred.

Standard, unipolar extremity and precordial leads taken on Sept. 9 display the expected progression of changes in the ventricular complexes (Figs. 1 and 2). The displacement of the RS-T segment has disappeared, and the T waves are now sharply inverted in Leads I, V_L, V_2, V_3, V_4, and V_5. Subsequent electrocardiograms, taken on Feb. 3 and July 7, 1944, are similar except that the changes in the T waves have regressed to some extent.

CASE 2.—A 53-year-old foreman was seen in the Heart Station on March 2, 1943. He was complaining of attacks of pressing, squeezing discomfort beginning in the right arm, extending to the upper right anterior part of the thorax and sternum, and occasionally to the right cervical region. The first attack occurred on Feb. 13, 1943, while he was sawing

wood. However, subsequent attacks were not closely related to exertion, and the pain awakened him frequently at night. The discomfort usually lasted five to thirty minutes. Nitroglycerin had been found to give relief. During the evening of March 1, he had five attacks of short duration.

In 1940, he had a transient left hemiparesis during an attack of "food poisoning." The blood pressure was found to be slightly elevated at that time. He had inflammatory rheumatism at the age of 3 years, and a gastroenterostomy for peptic ulcer at the age of 39 years. His father died of a "heart attack."

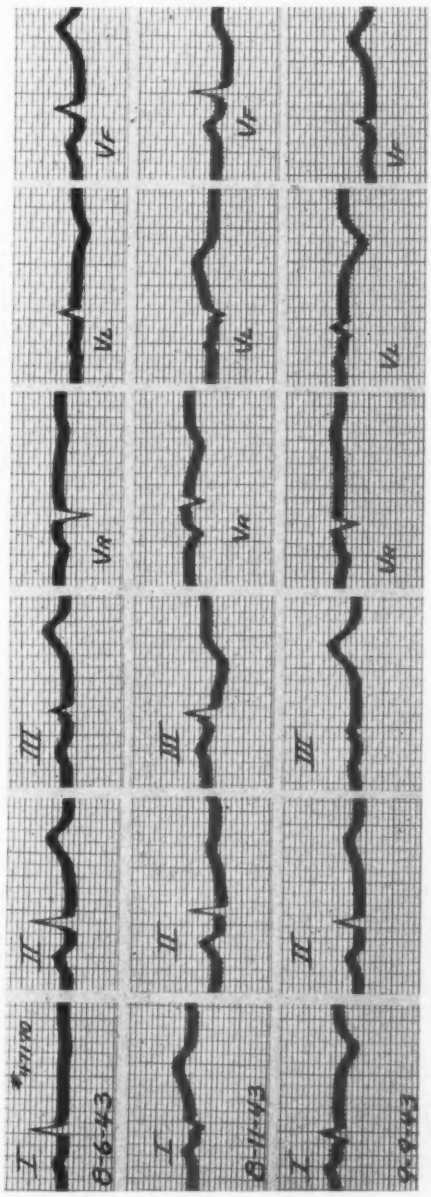

Fig. 1.—Case 1. Aug. 6, 1943: Standard leads and unipolar extremity leads taken six and one-half hours after onset of symptoms. Aug. 11, 1943: Standard and unipolar extremity leads four days after second attack. Sept. 9, 1943: Standard and unipolar extremity leads during convalescence.

Physical Examination.—The patient was a moderately obese, somewhat plethoric, middle-aged man. The heart was not enlarged. The aortic second sound was slightly accentuated. There were no murmurs or abnormalities of rate or rhythm. The blood pressure was 150/100. The remainder of the examination showed nothing of significance.

Laboratory Data.—The sedimentation rate was 9 mm. per hour (Wintrobe method). The miniature chest roentgenogram and the blood serologic reaction were negative.

Electrocardiograms.—The standard and unipolar extremity leads taken on March 2 show terminal inversion of the T waves in Leads I, II, and V_L, i.e., changes suggestive, but not diagnostic, of recent myocardial infarction (Fig. 3). The precordial leads taken at the same time display prominent QS deflections in Leads V_1, V_2, and V_E and deep terminal inversion of the T waves from all the precordial points explored (Fig. 3). These changes are characteristic of infarction of the anteroseptal portion of the left ventricular wall.[1]

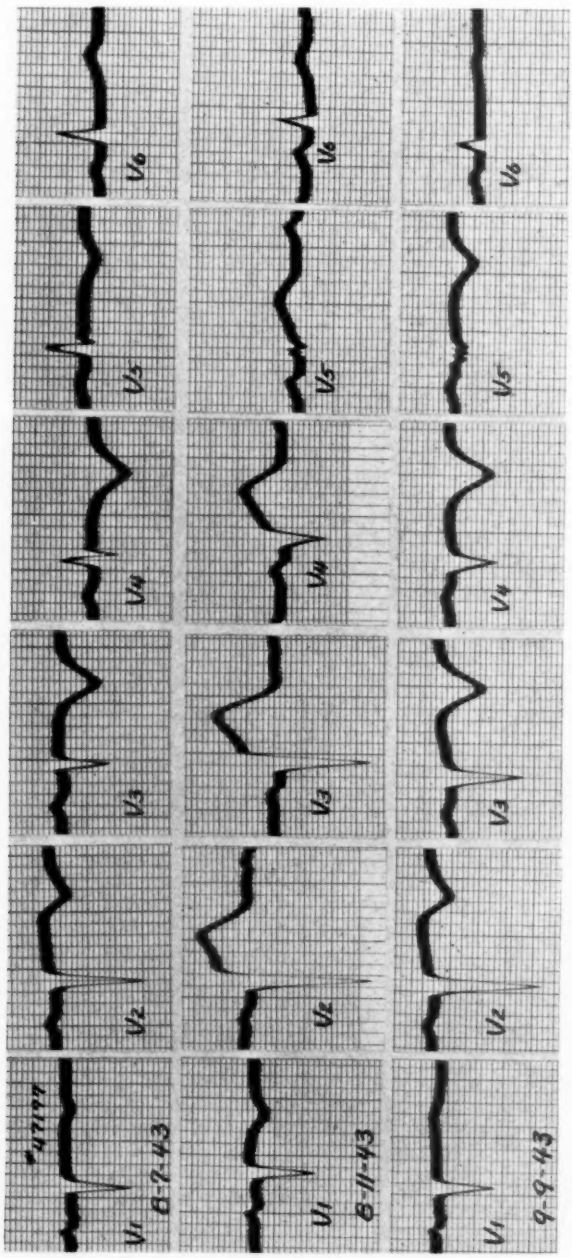

Fig. 2.—Case 1. Aug. 7, 1943: Precordial leads taken twenty-seven hours after onset of symptoms showing changes characteristic of recent anteroseptal myocardial infarction. Aug. 11, 1943: Precordial leads four days after second attack, showing evidence of lateral extension of the original lesion. Sept. 9, 1943: Precordial leads during convalescence, showing usual progression of changes.

Correlating these changes with the history, it seems probable that the infarction occurred during the preceding evening when the patient experienced the multiple, short attacks of anginal pain.

Second Admission.—After his first visit the patient was confined at home. On March 4, while in bed, he had an attack of pain in the right arm, thorax, and neck lasting eight hours. He took nitroglycerin tablets at intervals of five minutes (total of thirty tablets)

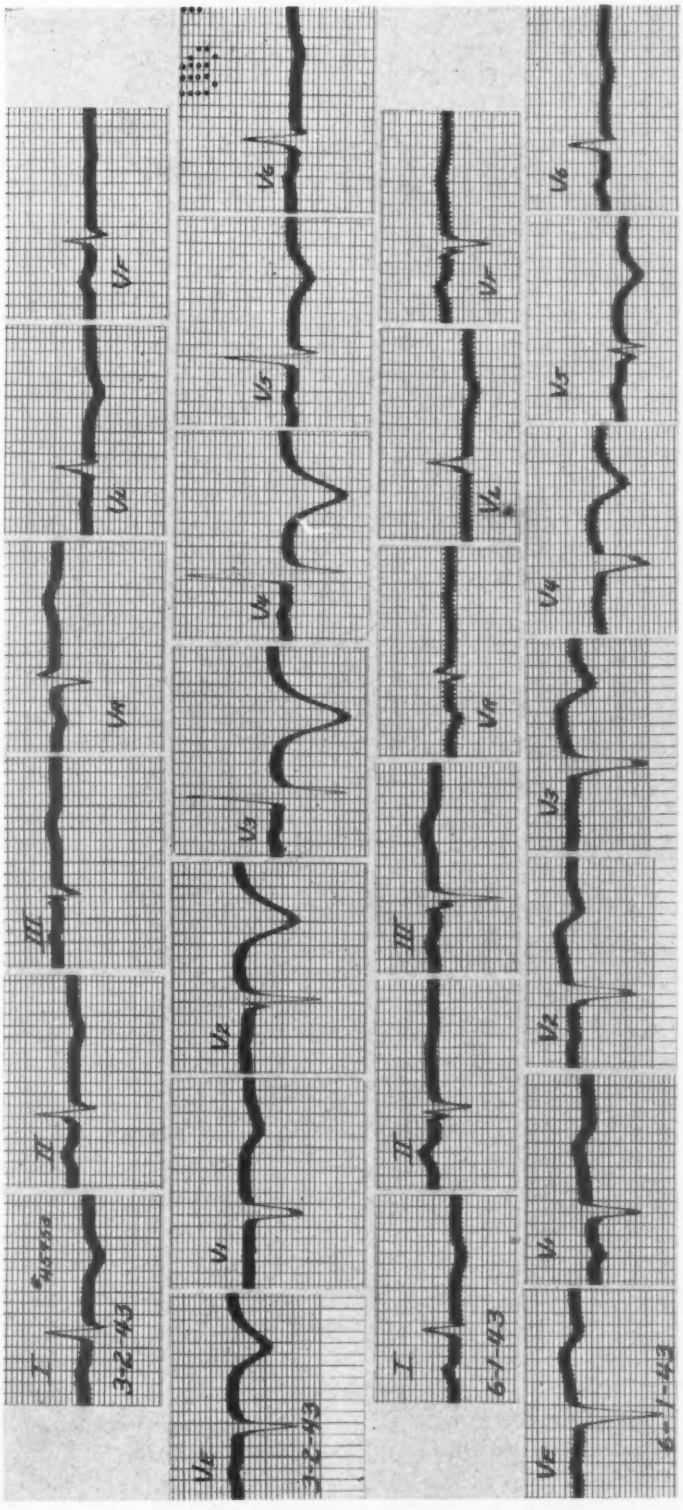

Fig. 3.—Case 2. March 2, 1943: Standard, unipolar extremity and precordial leads showing changes characteristic of recent anteroseptal myocardial infarction. Patient had five short, sharp attacks of anginal pain eighteen hours before. June 1, 1943: Standard unipolar extremity and precordial leads showing signs of the lateral extension of the initial infarct which probably occurred on March 4, 1943.

without obtaining relief. He remained in bed for five weeks and thereafter gradually resumed activity. He had no more prolonged attacks of pain, but mild anginal distress occurred on moderate exertion or excitement and was relieved by rest or nitroglycerin. He returned to the Heart Station for re-examination on June 1, 1943.

Physical Examination.—The findings were unchanged from those at the time of the first examination except that the heart sounds were rather faint. The blood pressure was 150/100.

Electrocardiograms.—Comparison of the standard and unipolar extremity leads taken June 1 with those recorded three months earlier discloses only minor changes. The R waves are smaller in Leads I, II, and V_F, the S waves are larger in Leads II, III, and V_F, and the T waves have become upright in Lead II (Fig. 3). The true significance of these changes becomes evident only when the precordial leads taken at the same time are examined (Fig. 3). QS deflections are now present in Leads V_1, V_2, V_3, V_4, and V_E. The T waves have become upright in Leads V_1 and V_E, but are again inverted in all the other precordial leads. A W-shaped QRS complex is now seen in Lead V_5 in which the initial ventricular complex was previously of normal form. It is evident that extension of the original anteroseptal infarct laterally to involve the anterior and anterolateral regions of the left ventricle was responsible for these changes. The history suggests that this extension occurred on March 4, when the patient had the prolonged attack of anginal pain.

DISCUSSION

These two patients are quite similar with respect to their history and the character and sequence of development of the electrocardiographic changes. In each case, the initial infarct was associated with relatively minor clinical manifestations and only T-wave changes in the standard and unipolar extremity leads (Figs. 1 and 3). The precordial leads, however, show characteristic QRS and T-wave changes due to anteroseptal myocardial infarction in the leads from the extreme right side of the precordium (Case 1, Fig. 2, Lead V_2, and Case 2, Fig. 3, Leads V_1, V_2, and V_E). The full import of the initial clinical manifestations might have been overlooked if multiple precordial leads, and particularly leads from the right side of the precordium, had not been taken. This becomes still more apparent if Leads V_4 and V_5 of the records taken after the initial infarct are examined; these display only T-wave inversion, which, albeit pronounced, in the absence of QRS changes, does not permit an electrocardiographic diagnosis of myocardial infarction. Therefore, it can be seen that standard limb leads and single precordial leads from the region of the cardiac apex would not have been as helpful in these cases as tracings of the type reproduced here.

The even greater value of multiple precordial leads in these two cases is seen upon examination of the precordial electrocardiograms taken after the second attack of severe pain (Figs. 2 and 3). Since the changes in the QRS complexes are now recorded from a much larger area, it is evident that the initial zone of infarction has grown larger by lateral extension. Although one could have suspected from the clinical picture that an extension of the original infarct or a second infarct had occurred, the exact situation was not revealed until the multiple precordial leads were repeated. In Case 1, these records were made soon enough so that acute injury effects were also recorded (Fig. 2), thereby further substantiating the impression that additional muscle had been infarcted. This was not possible in Case 2 because the second set of records was not taken early enough to show such changes.

In Case 1, the standard and unipolar extremity leads also showed significant changes when the infarct extended, particularly in Leads I and V_L. This is usually the case in anterior and anterolateral infarction, for these leads ordinarily reflect the form of the electrocardiogram in Leads V_5 and V_6. How-

ever, in Case 2, Leads I and V_L do not display changes of similar degree, although they do resemble Lead V_6. This difference is probably due to a slight difference in the position of the heart in the two cases. That this is true is supported further by the fact that, after the extension of the infarct in Case 2, the QRS complex in the unipolar lead from the left leg (V_F) showed greater change than that from the left arm (V_L).

Several recent reports have pointed out that "premonitory" or "prodromal" symptoms may precede myocardial infarction.[2-10] In both of the cases presented here, the symptoms accompanying the initial infarct were of the type which have been reported as frequently indicating "impending" infarction. Electrocardiograms taken on such patients during the interval between the onset of the prodromal symptoms and the occurrence of the myocardial infarct have usually been of normal form. However, in some of the records which have been published, there is inversion of the T waves in Lead I, in a single precordial lead, or in both, similar to that observed in the two cases reported here. On the other hand, in some cases of anteroseptal infarction (as shown by leads from the right side of the precordium, V_1, V_2, and V_3), the standard leads and precordial leads from the region of the cardiac apex (V_4, V_5, and V_6) are well within normal limits.[11] Therefore, if multiple precordial leads had not been taken, thereby revealing that anteroseptal infarction had already occurred, the two patients discussed here might also have been considered to have experienced only premonitory symptoms. The extension of the original lesion which occurred a few days later would then have been erroneously considered the initial infarction. The opinion that prodromal pain may actually be an expression of myocardial infarction in some cases has also been set forth by Dressler,[12] as well as by earlier observers.[3, 8, 10]

Bayley[13-15] has shown that the T-wave changes in patients with symptoms of impending infarction are the result of myocardial ischemia. He has presented important new evidence regarding the nature and manner of development of such changes. The alterations in the T waves which he has observed both clinically and in experimental animals are very similar to those recorded in the two cases presented here. However, the presence of significant QRS changes in the leads from the right side of the precordium in the records following the initial infarct indicate that, in addition to ischemia, actual infarction was present.

SUMMARY

Electrocardiographic studies are reported on two patients, each of whom had anteroseptal infarction, followed in a few days by lateral extension of the initial lesion. The worth of multiple precordial leads in the diagnosis of extension of such infarcts is illustrated.

Evidence is again presented that infarcts which are anteroseptal in location, as shown by diagnostic changes in leads from the right precordial area, often fail to produce equally significant changes in the limb leads.

It is suggested that, in cases of coronary arterial disease, some of the attacks of pain which have usually been considered prodromal symptoms of myocardial infarction, actually represent the development of a small, anteroseptal infarct, and that the more characteristic symptoms of acute coronary thrombosis which often occur later are due to an extension of this initial lesion. The true situation must be recognized, if such patients are to be properly treated.

We do not wish to convey the impression that we are convinced that all attacks of so-called prodromal pain represent actual myocardial infarction. The data, at present available, bearing on this problem are inadequate to justify this conclusion. Some attacks of this character appear to be due to acute processes developing in the coronary arteries or to transient myocardial ischemia associated with such processes.[7]

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THE MEASUREMENT OF THE LUNG-TO-FACE TIME BY AMYL NITRITE

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STUDY of the velocity of the blood flow has been of practical value in the last decade only, during which period simple methods have been devised for timing the blood velocity in clinical practice, and have thus enabled this fundamental hemodynamic factor to be taken from the experimental laboratory to the bedside of the cardiac patient. The common basis of all clinical methods for measuring the blood velocity consists in the introduction of an active physiologic substance into the circulation by intravenous injection. Then the time is measured from the moment of injection until the appearance of characteristic effects, which differ, according to the agent employed, in various but always constant parts of the circulation, and that is the circulation time. The end point reaction can be of a subjective nature (heat, taste, smell) or objective nature (optical registration of its occurrence by a characteristic color change in certain parts of the circulation [fluorescein[1]]; by a special detecting device if the substance employed is radioactive [radium C_2]; or by graphic registration if the provoked reaction is a cough or change in depth of breathing [lobelin,[3] papaverine[4]]). From another point of view the clinical methods of measuring the circulation time can be divided into partial or total methods, according to the circulation zone involved. The total methods of measuring the blood velocity comprise the sum of part of the venous, the pulmonary, and a certain part of the arterial, circuits. The partial methods indicate it within one zone only. For example, the ether method (Hitzig[5]) gives information about the condition of the circulation in the venous half only, i.e., from the antecubital vein to the arterial capillaries of the lung.

Compared with the partial methods, the number of total methods of measurement of the circulation time is quite large. Among the former, the most frequently employed agents for the measurement of venous circulation are ether and paraldehyde.[6] For the direct measurement of the lung-to-face time (apart from Gubner, Schnur, and Crawford's carbon dioxide method[7]), there are practically no other universally known procedures. In this paper, experiences with amyl nitrite as an agent for the direct measurement of the lung-to-face time will be described.

METHOD

The measurements were made on recumbent patients, after a rest period of ten minutes in a nonbasal condition. The amyl nitrite used in this study was obtained from ampules* which contain 4 minims of the drug and are covered by absorbent material. The time between the commencement of deep inspiration of the vapor of amyl nitrite and the appearance of a well-marked heat sensation in the face was registered by a centesimal chronometer, and represents the lung-to-face time as an expression of the trajectory from the pulmonary capillaries to the capillary bed of the face. Knowledge of certain peculiarities of the physiologic effects of breathing amyl nitrite vapors and adequate preparation of the patient for correct measurement are very important. Information must be given to lessen the possibility of nervous excitement before and during the process, in order to

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*Produced by Allen & Hanbury, of London.

prevent changes in respiration and circulation which may cause significant errors in the measurement. The inhalation must be made through the nose, with the mouth kept closed. In this way the mixture of air with the amyl nitrite vapor is less than it would be if the vapor were inhaled through the mouth. Consequently, before taking the measurement, it is necessary to make several tests of the patient's respiratory behavior. This is done by placing the unopened ampule directly under his nose and inviting him to take a deep and rapid breath, and then continue to breathe normally and quietly. Only after having made several trials, and being sure of the perfect collaboration of the patient, can the measurement be started. Attention must be drawn to the fact that the ampule explodes when opened. By this warning the perturbing effect can be lessened or avoided. Before the process is begun, the patient is informed that, several seconds after the first and only deep inhalation of amyl nitrite vapor, a definite sensation of heat will be felt in the face, together with a pounding of the pulses in the head and a certain feeling of heaviness and quickening of the heartbeat; these effects of the drug have no annoying intensity and will disappear within a few minutes. The patient is instructed to report immediately the first clearly felt sensation of heat in the face by uttering the word "Ya." That represents the end of the process. The measurement by chronometer begins with the first and only deep breath and ends with the first clearly felt heat in the face, indicated by the patient's saying "Ya." The chronometer is then stopped. It is not feasible to substitute observation of flushing of the face by the examiner for the subjective sensation of heat felt by the person under examination, because nervous excitement and emotion, by the psychovasomotor reflex mechanism, are able to produce similar flushes before the inhalation of the amyl nitrite, but with no definite feeling of heat. The other effects of inhalation of amyl nitrite vapor, such as cough, pounding of the pulse, and tears, are inconstant and not suitable for marking the end point of any measurement.

As a final observation about the technicalities of the measurement of the amyl nitrite circulation time (a.c.t.), the necessity of the patient's being recumbent during the test must be emphasized, in order to avoid incidents which may follow dizziness (faintness, even syncope).

RESULTS OF MEASUREMENTS IN 250 CASES

Normal Subjects (Table I).—In the group of one hundred normal persons, whose ages ranged from 16 to 70 years, with more than half between 30 and 50 years (58 cases), the amyl nitrite time varied between 14 and 25 seconds, with an average of 19.5 seconds, and the greatest number between 20 and 21

TABLE I. NORMAL SUBJECTS

A.C.T. (SEC.)	NUMBER OF CASES
14	7
15	8
16	7
17	6
18	7
19	9
20	14
21	12
22	9
23	9
24	7
25	5
Total	100
Average a.c.t. for normal subjects	19.5 sec.
Range	14 to 25 sec.

Relation of Age to A.C.T. in Normal Subjects

AGE (YRS.)	NUMBER OF CASES	AVERAGE A.C.T. (SEC.)
10 to 20	5	17.4
20 to 30	13	18.4
30 to 40	22	18.0
40 to 50	36	20.0
50 to 60	12	21.7
60 to 70	11	21.7
70 and over	1	24.0

seconds. The average amyl nitrite time in relation to each age group, classified with differences of ten years, enabled the recognition of the fact (previously established with different methods) that the velocity of the blood flow diminishes with increasing age. The average a.c.t. in the group of youngest persons was 17.4 seconds. In the groups of older persons the velocity showed a linear tendency to decrease, and a maximum of 24 seconds was recorded in the oldest group.

The intensity of the heat sensation was well marked in every case, and in the group of healthy persons it was possible to establish the fact that the intensity of the feeling of heat in the face was directly proportional to the velocity of the blood flow. A more intense sensation was felt in cases of higher velocity (shorter amyl nitrite time), and a milder one if the velocity of the blood was slower.

The most frequently observed (side action) was a slight degree of dizziness that disappeared completely in two to five minutes. Also, the frequent flushing of the face, with or without tears, induced in the patient a strange but not disagreeable feeling. The heart rate changes, as registered by the electrocardiograph and recorded simultaneously with the inhalation of the amyl nitrite vapor, were very different. In some cases the heart rate remained unchanged, but in the majority it increased forty to fifty pulsations per minute, then returned to the initial rate within one or two minutes. In the group of healthy persons the measurement was reliable in every case.

Decompensated Cardiac Patients (Table II).—The experience acquired in the examination of one hundred fifty patients with different degrees of heart failure reinforces the established correlation between the intensity of the warm sensation provoked by the inhalation of amyl nitrite vapor and the velocity of the blood flow. In general, the heat sensation in the faces of decompensated cardiac patients decreased with diminished blood velocity, and in advanced stages it was impossible to establish any reaction. Above an a.c.t. of 50 seconds, the warm sensation was very mild or practically imperceptible by the patient. The measured values of the a.c.t. of decompensated cardiac patients were larger than those of people in normal health, and a tendency existed, but not in a mathematical sense, to find a prolonged circulation time associated with cases of a more advanced degree of decompensation, judged by the sub-

TABLE II. DECOMPENSATED CARDIAC PATIENTS

NUMBER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG.)	VITAL CAPACITY (C.C.)	DYSPNEA	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	M. S.	64	150/ 80	1,800	+++	54	Arteriosclerotic heart disease
2	F. M.	60	120/ 80	1,900	+++	47	Arteriosclerotic heart disease
3	J. U.	60	130/ 50	2,000	++	45	Aortic insufficiency
4	M. E.	46	120/100	1,800	+++	45	Mitral valvular lesion
5	F. U.	78	110/ 60	3,400	+++	45	Aortic insufficiency
6	J. U.	60	130/ 50		++	40	Aortic insufficiency
7	R. N.	73	90/ 50	1,600	+++	39	Arterial hypertension
8	M. C.	60	200/140	1,000	+++	35	Arterial hypertension
9	M. R.	38	120/ 80		+++	35	Mitral valvular disease
10	N. G.	70	140/ 90	2,400	++	34	Arteriosclerotic heart disease
11	M. G.	55	90/ 70	2,600	++	34	Chronic myocardial infarction
12	I. P.	58	90/ 60	2,500	++	34	Arteriosclerotic heart disease
13	H. L.	59	150/ 10	3,100	+	34	Arterial hypertension
14	J. M.	64	120/ 60	1,600	++	32	Cor pulmonale
15	R. L.	63	120/ 90	1,600	++	32	Arteriosclerotic heart disease
16	G. F.	60	120/ 80	2,400	+	32	Arteriosclerotic heart disease
17	D. R.	62	140/ 80	3,200	++	32	Arteriosclerotic heart disease
18	A. B.	51	100/ 60	2,800	+	32	Arteriosclerotic heart disease
19	K. K.	42	120/ 70	3,000	+	32	Chronic myocardial infarction
20	A. P.	56	120/ 80	2,100	++	31	Arteriosclerotic heart disease

jective symptoms of shortness of breath and the objective findings of pulmonary and hepatic congestions and edemas. According to the experience acquired by the systematic application of amyl nitrite for the measurement of circulation time, the vital capacity is the objective sign which is most intimately related to the velocity of the blood flow. Diminished vital capacity, with other characteristic respiratory factors of cardiac origins that indicate pulmonary congestion and more enlarged cross section of the pulmonary vascular tree, was constantly accompanied by prolonged amyl nitrite circulation time. This correlation appeared evident not only by the comparison of the absolute values of vital capacity in different individuals, but especially in the same person in different conditions of compensation.

Compensated Cardiac Patients (Table III).—These cardiac patients showed an a.c.t. which was quite normal or slightly prolonged, with a normal or slightly diminished warm sensation. Among the different objective signs of heart failure, the parallelism between vital capacity and amyl nitrite circulation time was remarkable.

TABLE III. COMPENSATED CARDIAC PATIENTS

NUMBER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG)	VITAL CAPACITY (C.C.)	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	E. B.	31	100/60	2,100	27	Mitral stenosis
2	E. G.	31	110/70	2,700	27	Mitral stenosis and insufficiency
3	J. A.	48	130/90	2,600	25	Chronic myocardial infarction
4	J. F.	45	90/70	2,700	24	Angina pectoris
5	F. J.	56	120/80	3,000	23	Angina pectoris
6	S. U.	49	110/70	3,000	21	Angina pectoris
7	V. C.	65	100/70	3,100	20	Angina pectoris
8	A. H.	48	120/70	4,300	20	Aortic insufficiency
9	G. L.	56	140/80	3,400	18	Arteriosclerotic heart disease
10	J. B.	61	110/70	4,200	17	Chronic myocardial infarction

To illustrate this parallelism between the velocity of blood flow measured by amyl nitrite and the clinical aspects during different conditions of the compensation, the following cases are quoted:

CASE 1.—R. R., aged 73 years, was 166 cm. in height, and weighed 71 kilograms. He consulted his physician because of shortness of breath, dyspnea on exertion, insomnia, and nocturnal attacks of paroxysmal dyspnea. Physical examination revealed a slight degree of cyanosis, conjunctival jaundice, jugular ingurgitation, edema of the lower extremities, moist râles at the bases of both lungs, diminished heart sounds, and existence of a gallop rhythm. The liver was palpable for 4 fingerbreadths below the costal arch. The blood pressure was 90/50. Roentgenologic examination showed enlarged hilar shadows, pulmonary areas with congestive aspects, intense diminution of the transparency, and a certain amount of hydrothorax on both sides. The heart was generally enlarged with a greater preponderance of the left ventricle; the long diameter measuring 15 centimeters. The movements of the heart shadow were diminished. The electrocardiogram showed sinus rhythm with a heart rate of 92 per minute and with electrical left axis deviation. P_1 was positive; P_2 was isoelectric; and P_3 was negative. R_2 was notched; T_1 was negative; T_2 was isoelectric; and T_3 was positive. The S-T junction in Leads I and II was below the reference level and, in Lead III, was slightly above. PQ measured 0.20 second and QRS 0.10 second.

Diagnosis: myocardial damage, both auricular and ventricular, and signs of intraventricular conduction trouble. In this condition the vital capacity measured 1,600 c.c. and the a.c.t. was 39 seconds. Treatment was initiated immediately with strophanthin combined with aminophylline intravenously every day, to which one ampule of Esidrone was added every five days. After twenty days of treatment the patient improved noticeably and a control examination revealed no signs of pulmonary congestion. The liver was smaller (its inferior border was palpable 2 fingerbreadths below the costal arch), and the

edema of the legs had disappeared. The blood pressure rose to 115/50; the pulse rate diminished to 72 per minute. The vital capacity increased to 2,500 c.c., and the amyl nitrite circulation time was reduced to 17 seconds.

In the next two weeks the patient, against medical advice, took no medicines, a mistake which rapidly resulted in a severe setback, and a clinical examination showed him to be in the same condition as he was before treatment began. The vital capacity was exactly the same, i.e., 1,600 c.c. and the a.c.t. of identical value, 39 seconds.

CASE 2.—E. C., 60 years of age, had hypertension and congestive heart failure. She was suffering from shortness of breath, dyspnea on exertion, and a cough for more than ten years. Examination revealed that the patient had slight cyanosis in the face and ingurgitated veins in the neck with irregular pulsations. There was very pronounced anasarca in the legs. The liver was palpable at the level of the navel, and ascites was present. Ausculation revealed rare moist râles at the bases of the lungs, and the heart sounds were accentuated with a systolic murmur at the apex. The roentgenologic examination showed clear pulmonary areas with slight hydrothorax in the left side. The heart shadow was extremely enlarged, especially the left ventricle which was in contact with the thoracic wall. The long diameter was 22 cm.; the arch of the right auricle was pronounced; the shadow of the aorta was slightly enlarged; and the descendent segment was visible in the intrathoracic trajectory. The electrocardiogram showed auricular fibrillation with a ventricular rate of 100 per minute. There was a left axis deviation. R_1 was the predominant wave of the ventricular complex in the first lead and S_3 in the third lead; both were notched. T_1 and T_2 were negative, and T_3 was positive. The S-T junction was deeply depressed below the isoelectric line in the first, and above it in the third, lead. QRS measured 0.12 second.

Diagnosis: auricular fibrillation, left bundle branch block, and myocardial damage. The blood pressure was 180/120. The a.c.t. result in this condition was 32 seconds.

In the following twenty days treatment was begun with venesection, 600 c.c., strophanthin with aminophylline intravenously in combination with salyrgan every four days. The patient was feeling much better and the objective signs of the decompensation were reduced. In this improved condition of compensation the circulation accelerated and measured 23 seconds by amyl nitrite. During the next month the strophanthin was replaced by digital but with no satisfactory results, and the patient returned with marked dyspnea and periodic breathing; the edemas also reappeared. The result of the measurement of the circulation time, in the patient's impaired condition, was 35 seconds.

In this observation the a.c.t. was a true indicator of the altered condition of the circulation and showed parallelism with the clinical aspect.

CASE 3.—E. G., 50 years of age, weighed 74 kg. and was 172 cm. in height. Eight years previously he had suffered from an attack of rheumatic fever and since then had begun to notice shortness of breath and pain in the chest without irradiation. The physical examination disclosed a pale patient with visible arterial pulsation in the neck. The liver was palpable 2 fingerbreadths below the right costal margin. The apex impulse was palpable in the sixth intercostal space in the anterior axillary line. Moist râles were heard at the bases of the lungs posteriorly. Over the aortic focus an intense sisto diastolic murmur was heard, which was transmitted to the large vessels. The roentgenologic examination showed an enlarged heart shadow in "aortic configuration," and the heart measured 18.7 cm. in length. The electrocardiogram showed sinus rhythm with a heart rate of 96 per minute. Left axis preponderance was present, S_3 biphasic, T_1 and T_2 negative, and T_3 isoelectric. The S-T segment was displaced to below the isoelectric level. Arterial pressure was 120/60, vital capacity, 1,600 c.c., and the a.c.t., 28.5 seconds. Treatment was begun with digitalis, and the patient improved after twenty days, when the a.c.t. reached 24 seconds. Three months later the patient's condition was improved further still, and the vital capacity was 2,200 c.c. and the a.c.t., 20 seconds.

In this case the clinical improvement and the changes in vital capacity and circulation time clearly demonstrate parallelism.

CASE 4.—M. G., aged 60 years. Clinical diagnosis: chronic myocardial infarction and cardiac insufficiency. Three years previously he had suffered coronary thrombosis, and, since then, he had noticed shortness of breath, which had become more intense. Physical examination showed congestion of the lungs and diminished heart sounds. There was a loud systolic murmur heard over the apex area. The inferior edge of the liver was pal-

pable 3 fingerbreadths below the right costal margin. Roentgenologic examination detected a generally enlarged heart shadow with a preponderance of the left ventricle and a longitudinal diameter of 18.5 centimeters. The electrocardiogram showed sinus rhythm with a heart rate of 75 per minute. Electrical axis deviation was absent. Q_2 and Q_3, were deep with notching; T_1 and T_2, were isoelectric; and T_3, was negative. In the precordial Lead CF_4 a small R wave was present, not larger than 1 millimeter. T was positive and the S-T junction was elevated above the zero line. PQ measured 0.20 second and QRS, 0.10 second. The electrocardiographic signs described indicate myocardial damage as in cases of chronic myocardial infarction of the anterior wall of the left ventricle. The measured vital capacity was 2,600 c.c., and the a.c.t. was 34 seconds. After being treated for a month with strophanthin and deriphyllin intravenously, the patient was noticeably improved. A repetition of the same examination resulted in 3,000 c.c. for the vital capacity and 29 seconds for the amyl nitrite time—an improvement in both factors.

CASE 5.—J. V., 49 years of age, had rheumatic heart disease with mitral stenosis and cardiac insufficiency. His chief complaints were shortness of breath, palpitation, and swelling of the abdomen. Râles were present in both lung bases; the heart rhythm was totally irregular, rate, 100. There was an accentuation of the first sound over the apex and a diastolic murmur. The second sound was accentuated over the pulmonary area. The roentgenologic examination detected a cardiac enlargement in all diameters with mitralization and an enlargement of the pulmonary vessels with diminished transparency of the pulmonary areas. The electrocardiogram showed auricular fibrillation, no electrical axis deviation, an isoelectric T_1, a flattened T_2, and a positive T_3. In the precordial Lead CF_4 there was a profound displacement of the S-T intervals below the isoelectric line. The blood pressure was 90/60; the vital capacity was 2,500 c.c.; and the circulation time, measured by amyl nitrite, was 30 seconds. The treatment employed consisted in taking digital in intermittent form combined with one injection of salyrgan weekly, which brought the patient to a satisfactorily improved condition, and, four months later, the tests taken showed a vital capacity of 3,000 c.c. and an a.c.t. of 19 seconds.

CASE 6.—K. K., aged 45 years, weighed 89 kg. and was 191 cm. in height. He had arterial hypertension and complained of high blood pressure, nervousness, and slight shortness of breath on exertion. The clinical examination revealed a normal lung condition, and the heart sounds were clear and of normal intensity. Roentgenologic examination showed enlargement of the heart shadow to the left with a longitudinal diameter of 16.5 centimeters. The electrocardiogram showed a sinus rhythm of 60 contractions per minute with pronounced left axis deviation. T_1 was negative; T_2 and T_3 were positive; and the S-T_1 interval was deeply displaced below the isoelectric line. The auriculoventricular conduction time was 0.20 second, and QRS was 0.10 second. These electrocardiographic findings were as usual in cases of marked hypertrophy of the left ventricle as in hypertensive heart disease. The arterial blood pressure was 170/120, the vital capacity, 4,000 c.c., and the a.c.t., 37 seconds. The treatment prescribed consisted of small doses of digital continuously, combined with tablets of aminophylline and phenobarbital. The patient came back after three months, reported improvement, and examination at that time revealed an arterial pressure of 150/110, a vital capacity of 4,500 c.c., and an a.c.t. of 29 seconds.

In all these observations, according to the clinical improvement, the objective signs of a better circulation as well as the vital capacity and the amyl nitrite circulation time showed parallelism, i.e., values nearer to normal.

Acceleration of the Circulation (Table IV).—In this small group of patients who clinically showed multiple evidence of hyperthyroidism the a.c.t. was definitely shortened, rising to 8 seconds, which is equal to one-third of the normal value, i.e., there exists a strongly accelerated circulation. In these cases the intensity of the heat sensation in the face was very sharp. There was burning, intense flushing, pronounced tears, violent palpitation—not only in consequence of hemodynamic causes (greater concentration of amyl nitrite vapors in the peripheral blood following a more rapid transportation by the accelerated circulation)—but because, in this condition, a greater nervous excitability exists. However, this undesirable side action of amyl nitrite, apart from the nervous impression, causes no serious trouble. In regard to the correlation of the velocity

TABLE IV. ACCELERATION OF THE CIRCULATION

NUMBER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG)	VITAL CAPACITY (C.C.)	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	G. A.	34	150/90	3,200	8	Hyperthyroidism
2	N. B.	27	140/60	3,600	10	Hyperthyroidism
3	A. G.	30	100/70	3,000	11	Hyperthyroidism
4	J. O.	33	90/50	3,500	12	Hyperthyroidism
5	G. B.	44	100/70	3,800	13	Hyperthyroidism

of the blood flow to the vital capacity, the observation can be made, that notwithstanding the fact that the vital capacity shows normal values, the cyphers that were found represented the minimal variation within the proportional. There are certain divergences between the relative high speed of the blood flow and the relative low amount of air expressed by the vital capacity.

Pulmonary Emphysema (Table V).—In this characteristic group of patients who complained principally of shortness of breath and dyspnea on exertion, and in whom the clinical examination revealed no evidence of cardiac disease, or only in such a slight degree that it did not elucidate their intensive reduction of the functional capacity, and who generally showed a significantly diminished vital capacity, the amyl nitrite circulation time was perfectly normal or slightly prolonged. Although the amyl nitrite vapors inhaled were only a fraction of the amount normally introduced, as a result of the reduced respiratory air volumes, the intensity of the warm sensation in the face was perfectly normal in these cases of pulmonary emphysema. Among them it is impossible to recognize a parallelism between the vital capacity and the circulation time because very different values of vital capacity can be associated with an identical value of blood velocity. The experiments made by measurement with amyl nitrite affirm the integrity of the circulation in cases of bronchial asthma or emphysema where the cause of the shortness of breath is due to pulmonary (respiratory) factors and not to circulatory failure. Of course, if the emphysema is of long duration, or if it comprises the heart, the amyl nitrite time will be prolonged as in any other case of heart failure.

The normal intensity of the warm sensation in emphysematous patients demonstrates that the amount of amyl nitrite vapors inhaled in one breath is sufficient for its production, and a greater quantity does not provoke a shortening of the amyl nitrite circulation time.

TABLE V. PULMONARY PATIENTS

NUMBER	NAME	AGE (YRS.)	BLOOD PRESSURE (MM. HG)	VITAL CAPACITY (C.C.)	A.C.T. (SEC.)	CLINICAL DIAGNOSIS
1	I. D.	57	160/ 90	1,000	22	Bronchial asthma, emphysema
2	A. P.	62	110/ 80	1,000	25	Emphysema
3	A. K.	60	130/100	1,100	26	Emphysema
4	C. B.	54	120/ 70	1,200	22	Bronchiectasis, emphysema
5	E. D.	28	130/ 90	2,100	15	Bronchial asthma
6	E. Q.	46	120/ 80	2,200	22	Emphysema
7	E. S.	54	120/ 70	2,200	19	Tuberculosis, chronic fibrosis
8	F. V.	70	140/ 90	2,200	27	Chronic bronchiectasis, emphysema
9	F. S.	68	130/ 90	2,200	23	Emphysema
10	J. S.	55	140/100	2,300	21	Emphysema

Duplicate Measurement (Table VI).—In several cases duplicate measurements were taken. A second test was made ten minutes after the first one, without any noticeable discomfort to the patient. The results of the second measurement were identical with the first in the majority of cases, or differences were

TABLE VI. DUPLICATE MEASUREMENTS

NUMBER	FIRST MEASUREMENT (SEC.)	SECOND MEASUREMENT (SEC.)	DIFFERENCE (SEC.)	CLINICAL DIAGNOSIS
1	29	29	0	Arteriosclerotic heart disease
2	22	22	0	Normal
3	19	21	2	Thyrotoxic heart disease
4	45	47	2	Arteriosclerotic heart disease
5	32	35	3	Arteriosclerotic heart disease
6	24	27	3	Arteriosclerotic heart disease
7	24	28	4	Arteriosclerotic heart disease
8	39	34	5	Arterial hypertension
9	24	19	5	Normal
10	17	25	8	Normal

registered of between two to five seconds only. In some rare instances the differences were larger. This inconstancy of amyl nitrite measurement (which has also been observed in other methods such as Lilienfeld and Berliner[3]) is a peculiarity not yet explained, neither by the methods nor by the circulation itself.

Comparative Measurement With Other Methods (Table VII).—In a small group of ten healthy persons simultaneous measurements were made of the arm-to-tongue time by calcium bromide[8] (1 c.c. of 50 per cent Br. 2 Ca.), the arm-to-lung time by ether, and the lung-to-face time by amyl nitrite. The results of these simultaneous measurements by different methods gave concordant values, i.e., normal for each system of determination, but it was not possible to find numerical equivalents between the different methods employed. The calculated value of lung-to-face time, i.e., the indirect determination of the functional capacity of the left ventricle will be obtained by subtracting the ether time from the total circulation time (the calcium bromide time), the remainder being the lung-to-face time. In each case observed, the number of amyl nitrite seconds equivalent to the corresponding number of calcium seconds was always different. However, the same criticism may be justly applied, in general, to all systems of measuring circulation time, because it is erroneous to consider as equal one second of ether time and one second of calcium, decholin, histamine, or amyl nitrite time.

TABLE VII. COMPARATIVE MEASUREMENT OF THE VELOCITY OF BLOOD FLOW IN NORMAL PERSONS

NUMBER	NAME	AGE (YRS.)	AMYL NITRITE (SEC.)	CALCIUM BROMIDE (SEC.)	ETHER (SEC.)
1	G. C.	16	24	13	7
2	M. A.	45	22	12	7
3	H. A.	22	22	12	7
4	Z. C.	30	20	12	8
5	F. O.	29	21	13	7
6	D. C.	42	21	17	6
7	C. P.	30	20	14	8
8	G. P.	46	20	13	7
9	F. S.	29	18	15	8
10	E. C.	16	16	10	8

Impracticable Measurement.—In the series of one hundred fifty cardiac patients the measuring of the circulation time by amyl nitrite failed in seven cases. Five of these were cardiac patients in a condition of severe decompensation with intense pulmonary engorgement and edemas. Either the heat sensation in the face was very feeble so that the patient hardly felt it, or it was simply absent. A repetition of the measurement on the same day gave an identical

result. After commencing adequate treatment, new measurements were taken when the conditions had improved and showed, according to the degrees of decompensation, a prolonged but definite circulation time. The other two patients were individuals who betrayed slight mental symptoms, such as depression, because of intense edema and slight uremic retention, respectively. In these cases satisfactory mental collaboration was not obtained.

Incidents.—In the case of a patient suffering from acute glomerulonephritis with a blood pressure of 200/120, a very intense headache appeared after he had inhaled the amyl nitrite vapors and marked a circulation time of 26 seconds. The headache lasted for ten minutes and passed away without any consequences. This headache also appeared in other cases of hypertension, but in a milder degree. Consequently, in order to avoid this inconvenience, measurement has been omitted in cases where the blood pressure is higher than 200.

DISCUSSION

Amyl nitrite, introduced into therapeutics by Brunton,[9] in 1867, has been studied intensely in order to explain the mechanism of its action. According to the actual stage of our knowledge, the vasodilation produced by the inhaling of its very volatile vapors is caused by its direct action on the unstriated muscle of the peripheral vessels, both arteries and veins. Cushny[10] pointed out that the peripheral effect of the amyl nitrite can easily be demonstrated by experiments made on the amputated legs of animals—the amount of perfusion liquid that was leaving the vein rose immediately if some drops of this substance were introduced with the liquid of perfusion into the artery of the amputated leg. The appearance of flushing and heat in the face indicates the arrival of the blood containing amyl nitrite at the vascular territory of the face and thus represents the end point of the measure. The run of the amyl nitrite inhaled begins with the respiratory tract, from the trachea to the alveoli, where it reaches the extensive capillary bed of the lungs and is absorbed. From the pulmonary capillaries the veins of the lungs carry it to the left heart and from here it is taken to the arterial circulation.

Evidently the expression amyl nitrite circulation time does not mean exclusively the objective time duration of the blood movement from the initial point to the end of the trajectory, but it represents the sum of different subtimes, among which the most important are (1) the duration of one deep inspiration, (2) the velocity of absorption through the alveolar membrane, (3) the time required for the transfer of the blood from the pulmonary capillary area to the vascular bed of the face, (4) the time required to produce the warm sensation, (5) the time of the psychomotor reaction of the patient, indicating the presence of the warm sensation, and (6) the time of the psychomotor reaction of the observer who is recording the circulation time.

The decisive factor in determining the numerical value of the circulation time is, without doubt, the real circulation time, i.e., the duration of the circulatory movement of the blood from the initial point to the end point of the trajectory, while all the other factors mentioned are of secondary importance. The duration of a deep breath, determined in many cases, ranged between 1 and 1.5 seconds following the introduction of the amyl nitrite vapors into the circulation by a deep breath required identical times as the intravenous injection of 1 or 2 c.c. of an aqueous solution employed for the measurement of the circulation time. The condition of the nervous state, especially the clear sensorium, whose influence we cannot appreciate quantitatively, must, nevertheless, be attended to.

The amyl nitrite circulation time must be considered as the average value of the *fastest* transport of blood from the pulmonary capillaries to the minute vessels of the face. It is a peculiarity of the amyl nitrite measurement that the amount of vapors inhaled is not exactly dosed, but experience demonstrates that the amount of amyl nitrite vapors inhaled by a deep breath is more than sufficient to provoke a definite sensation of warmth in the face, because, in conditions of bronchial asthma or emphysema, the amount of air inspired is only a third or a fourth of the normal, yet the appearance of the heat sensation occurred in times and intensity considered as normal, too. A larger amount of amyl nitrite by forced deep inspiration did not shorten the appearance of the warm sensation, but it did reinforce its intensity. According to all these considerations, the most rapid and the most intense warm sensation will be observed in hyperthyroidism, where the effective rapid blood velocity allows the arrival of amyl nitrite, inhaled in normal amounts, in higher concentrations in the periphery and to all these hemodynamic reasons must be added the increased nervous sensitivity, characteristic of this condition, that reinforces the intensity of the warm sensation. The inverse takes place in heart failure. The amount of inspired amyl nitrite is diminished following the decreased respiratory volume, the velocity of the blood flow is less, and the concentration of amyl nitrite in the blood is lower, not only as a consequence of the slower circulation, but also on account of the higher degree of dilution determined by the increased amount of blood contained in the enlarged cross section of the pulmonary vascular bed.

The close relation existing between the a.c.t. and the vital capacity indicates the importance of the state of the pulmonary circulation, the degree of opening, and blood repletion to the velocity of blood flow. The experiences with measurements of amyl nitrite indicate the tendency of a parallelism in different persons showing fastest circulation in cases of increased values of vital capacity, while the repeated measurements in the same individuals during treatment of decompensation corroborate the same observation. The changes of the width of the cross section of the pulmonary vascular tree and the changes of their blood content unquestionably are the most important factors for the delay of circulation in regard to the trajectory measured by amyl nitrite. The suggestions of Nylin[11] about the importance of intracardial residual blood as a retarding factor for the circulation has been studied in the present work. The heart volume was estimated radiologically by the Rohrer-Kahlstorf[12] method, without possibilities of establishing correlation in a definite sense between cardiac volume and circulation time because the heart volumes were greatly enlarged (f.i. 1,250 c.c. or more) with normal shortened circulation time (17 seconds [a.c.t.]). But it seems without question that this new point of view of the intracardiac congestion with the resulting increased volume of residual blood represents another possibility for hemodynamic interpretation of prolonged circulation time.

The circulatory trajectory measured by amyl nitrite corresponds properly to the left ventricle. However, based on the results of amyl nitrite measurement, an accurate differentiation between left or right ventricular failure is impossible, because the same values of circulation times can be observed in both cases. The multiple biologic compensations between the hemodynamic factors of the circulation can neutralize partial effects, thus compensational adaptive changes of systolic output, circulatory blood volume, cross section of the vascular bed, and even functional short circuits can determine great individual variability in the resulting value of circulatory velocity. In cases of slight decompensation, precisely within the compensatory capacity of the

circulation, the a.c.t. can remain perfectly normal or scarcely prolonged and only if the degree of heart failure overwhelms the compensation capacity of the circulation will it be prolonged. As a matter of fact, in the clinical picture there was no parallelism between the intensity of subjective discomfort, especially shortness of breath, and prolongation of a.c.t., but it is true that in advanced cases of decompensation the a.c.t. never was normal and in normal conditions of the circulation the amyl nitrite measurement never was prolonged. For all these reasons, as much theoretical as practical, the value of the measurement of the circulation time must be interpreted individually.

SUMMARY

1. A new method for the measurement of the lung-to-face circulation time, using amyl nitrite as an agent, is outlined. The technique of administration is described, and normal values and their correlations are established. The method is simple, needs no apparatus nor assistants, and can be performed by the examiner alone.

2. The amyl nitrite circulation time (a.c.t.) measures the functional capacity of the left ventricle and is determined essentially by the condition of the pulmonary circulation recognizable by the vital capacity. There exists a tendency of parallelism as much in the absolute value of both factors as especially in their modifications in different conditions of compensation in the same person.

3. The inverse correlation is established between the a.c.t. and the intensity of the warm sensation: more intense heat with shortened circulation time and vice versa.

4. In conditions of heart failure, the a.c.t. is prolonged, and the intensity of the warm sensation is diminished, but there is no strict parallelism with the clinical features.

5. In hyperthyroidism the a.c.t. is shortened and the intensity of the warm sensation is strongly reinforced. Emphysema or bronchial asthma, not complicated by heart failure, are characterized by normal a.c.t. and normal intensity of the warm sensation.

6. Subminimal a.c.t., except for existing intracardial or arteriovenous short circuits, never is observed *with* cardiac failure; largely prolonged a.c.t. never is observed *without* heart failure. Medium values of a.c.t. are as compatible in persons of normal circulation as in those with slight failures of it.

7. A differentiation between left or right ventricular failure is not possible, based upon the amyl nitrite measurement.

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COARCTATION OF THE AORTA

Report of Two Cases, Relating Clinical Data to Degree of Constriction Measured at Autopsy, With a Method of Standardization for Related Measurements

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THE following two cases illustrate the difficulty sometimes encountered in the diagnosis of aortic coarctation. Both represent modes of death that are not common in this disease.

CASE REPORTS

Case 1.—This 20-year-old white man is known to have been rejected by the Armed Forces in February, 1943, because of hypertension (systolic blood pressure about 180). Several months before death he was examined at this clinic because of abdominal pain, nausea, and vomiting. At that time his blood pressure was 160, systolic, and 70, diastolic. Four weeks before death, in January, 1944, he was admitted with complaints of frontal headaches, facial edema, and dimness of vision. He told about an episode of chills and fever followed by joint pains, occurring late in 1943, and recurring about one month later, accompanied by hematuria and nocturia. At that time he noted small, painful, red nodules on his legs.

Physical Examination.—The patient was a pale, undernourished young adult with moderate, generalized edema. On his breath was a uriniferous odor. The left border of the heart extended 11.5 cm. to the left of the midsternal line in the fifth intercostal space. A blowing systolic murmur was heard best in the mitral area. The second aortic sound was louder than the second pulmonic sound. The liver was palpable 3 fingerbreadths below the costal margin.

The blood pressure was taken in all extremities. It was 30 degrees higher, systolic, and 5 to 15 degrees higher, diastolic, in the arms than in the legs. Throughout his illness the right brachial pressure averaged 180, systolic, and 90, diastolic. Comparison of brachial and crural pulses was not made.

Pertinent laboratory data appear in Table I. The patient was treated for his obvious kidney ailment, to which his hypertension was thought to be related. For most of his course, his temperature was subnormal; it was definitely not septic. No blood cultures were taken. The highest temperature reading was 38.5° C. He died on the twenty-fourth hospital day in circulatory failure and uremia.

Autopsy (Duke 3981).—The heart weighed 470 grams. The dilated left ventricle was 2 cm. thick. On both sides of the interventricular septum was a dense, white endocardial thickening, closely related to the septum fibrosum, suggesting late closure of a ventricular septal defect. The aortic valve was bicuspid. No other intracardiac anomalies were present. The measurements of significance regarding the heart and aorta are given in Table II.

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TABLE I. LABORATORY DATA

DATE ADMITTED	B.P.	ECG	HGB.	R.B.C.	W.B.C.	SED. RATE	N.P.N.	MICR. URINE*	BL. CUL.†	WT. (LB.)
					Case I					
Jan. 1944	180/90	Slight left axis deviation	6.5	61 M	10,800	15	153-210	2 to 3 W.B.C./HPF‡ 5 to 20 R.B.C./HPF	None	–
					Case II					
Sept. 1943	140/80	Slight left axis deviation	10.4	3.43 M	4,160	26	28	Neg.	Alpha Streptococci (3x)	133
Oct. 1943	150/70	Slight left axis deviation	11	3.73 M	7,240	0	30	1 to 4 W.B.C./HPF	Alpha Streptococci (3x)	125
Feb. 1944	130/70	Slight left axis deviation	6.1	1.63 M	5,200	14	24	5 to 20 W.B.C./HPF 10 to 25 R.B.C./HPF	Alpha Streptococci (3x)	121

*Microscopic study of urine.
†Blood culture.
‡High-power field.

The great branches of the aortic arch were situated in normal relation to one another. The ostium of the left subclavian artery was considerably enlarged. Two centimeters below this, just at the level of the aortic end of the ligamentum arteriosum, there was a 2 mm. thick diaphragm with a central opening having a circumference of 1.5 centimeters. The right half of the aorta, distal to the coarctation, was covered with large, friable vegetations. These proved to be attached to thrombotic material within an aneurysm 4 by 3 cm. in diameter. The second right intercostal artery was found on the inferior wall of the aneurysm, but the first right intercostal artery was lost in the aneurysmal formation. Cultures from purulent material in the aneurysm grew alpha streptococci. The outer limit of the aneurysm was formed by the esophageal wall, considerable destruction of which was evident grossly and microscopically. The iliac arteries were not dilated.

No other bacterial aneurysms were encountered. Clear fluid was found in all serous cavities (2,000 c.c. in the abdomen). Old and new infarcts marked the soft, flabby spleen (weight, 250 grams) and the gray-yellow kidneys. The latter were speckled with hemorrhages and, microscopically, showed a marked degree of damage from subacute diffuse and embolic glomerulonephritis.

TABLE II. STANDARDIZED MEASUREMENTS

	NUMBER MEASURED	MEAN (CM.)	STANDARD DEVIATION	STANDARD ERROR	CASE I (CM.)	CASE II (CM.)
Left ventricular wall	9	1.53	.260	.062	2.0	2.0
Aortic ring, circumference	8	6.35	.247	.064	6.0	6.0
Aorta 2 cm. from base	9	5.82	.598	.143	5.0	6.0
Innominate ostium	9	2.87	.558	.133	2.8	3.8
Subclavian ostium	9	2.03	.297	.071	3.5	1.5
Aortic circumference at subclavian artery	10	4.38	.299	.068	3.5	2.5
Coarctation circumference	--	---	---	---	1.5	2.0
Aorta at fourth intercostal artery	10	4.21	.227	.052	5.0	4.0
Aorta at seventh intercostal artery	10	3.97	.224	.051	3.4	3.5
Aorta at eleventh intercostal artery	10	3.60	.279	.063	2.8	3.6
Aorta at bifurcation	8	2.90	.471	.119	2.1	3.0

Anatomic Diagnosis.—Coarctation of aorta, adult types; bicuspid aortic valve; hypoplasia of abdominal aorta; cardiac hypertrophy and dilatation; chronic passive congestion of lungs; pulmonary edema; bilateral hydrothorax and ascites; chronic passive congestion of liver. Bacterial endocarditis (alpha streptococcus) with local extension through aortic wall into esophagus, mediastinal abscess, and acute mediastinal lymphadenitis; acute splenic tumor; bacteremia (alpha streptococcus); splenic and renal infarcts; subacute diffuse glomerulonephritis.

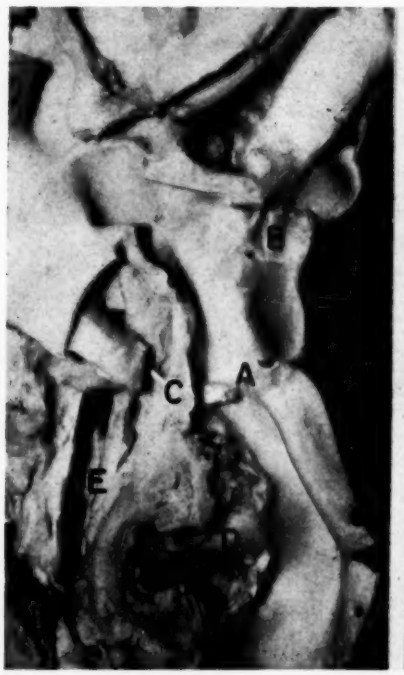

Fig. 1.

Fig. 2.

Fig. 1.—Case 1. The aorta is opened from the back to show the coarctation (A) at the level of the aortic end of the narrow ligamentum arteriosum (C). The aortic bacterial aneurysm (D) is below the coarctation, at the left side in the photograph. Its relation to the esophagus (E) is shown. The dilated ostium of the subclavian artery (B) is 2 cm. above the diaphragm of the coarctation.

Fig. 2.—Case 2. The aorta is opened from behind to show the constricting band (A) of the coarctation running from the caudal edge of the stenosed subclavian ostium (B) to the aortic end of the broad ligamentum arteriosum (C). The aortic bacterial aneurysm (D) is below the coarctation, at the left side in the photograph.

Case 2.—A 22-year-old white man was observed over a six-month period. During this time blood stream alpha streptococci were repeatedly grown. At the age of 6 years the diagnosis of weak heart had been made and limitation of activity imposed because of precordial pain and dyspnea on exertion. Two brothers and four sisters and both parents were entirely free of cardiovascular complaints. The patient was accepted for Army service in 1940. In the winter of that year, during a period when his infantry company was housed in tents (North Carolina), this man suffered four or five episodes of dull precordial pain and swollen, painful joints. These episodes lasted seven to ten days. Transfer to Panama alleviated his suffering with the result that final discharge from the Army was postponed until 1941, following an exacerbation of symptoms. He suffered six additional episodes before his first admission to Duke Hospital in September, 1943. For three months he had been uncomfortable with diurnal, afternoon fever. His temperature was 39° C.

Alpha streptococci were grown from his blood, and he was treated with sulfamerazine combined with fever therapy. This therapy produced only temporary sterility of the blood as judged by repeated cultures. In mid-October he was discharged. Twenty days later he reappeared complaining of sudden mid-epigastric pain which had persisted for five days as a dull ache. A sudden bout of right, lower quadrant pain, with rebound tenderness and a rise of 6,000 in his leucocyte count within twenty-four hours, led to exploratory celiotomy and removal of a normal, retrocecal appendix. The surgeon's note read: "There was no

evidence in the mesentery of the bowel of any thrombosis. Thorough search had been made." Several weeks postoperatively he was discharged, unimproved, but no longer suffering any severe local symptoms.

In February, 1944, ten days before death, he returned, complaining of precordial and epigastric pain, swollen legs, and puffy face. Sudden, sharp, knifelike, precordial pain had occurred in January, persisting as a dull ache with remissions and exacerbations. Occasional sharp pains in the pit of the stomach had troubled him. Joint pains recurred in early February and were accompanied by peripheral edema, an entirely new symptom.

Physical Examination.—The patient was an obviously ill, emaciated young adult with slight cyanosis, marked pallor, and facial edema but no petechiae. The lungs were clear. The heart was moderately enlarged to the left. No thrills were palpable. A loud systolic murmur was audible over the entire precordium, maximally at the left sternal border, particularly in the pulmonic area. The second aortic sound was louder than the second pulmonic. The tense abdomen was ubiquitously tender, and the liver edge was palpable just at the costal margin. The spleen and kidneys were not palpable. The right knee and ankle were tender on palpation and on voluntary motion. There was slight edema of the lower extremities.

The blood pressure was not taken in the lower extremities at any time during the patient's three admissions. There was never any comparison of brachial and crural pulses. Table I records the blood pressure (right arm) and pertinent laboratory findings for the three admissions. The temperature ranged daily from a low 37° C. at 8 A.M. to 39° C. at 4 P.M. during the first two admissions, but it never rose above 37.8° C. during the last admission.

The spleen became palpable several days before death. Twenty-four hours before death persistent nausea and vomiting began. Complaints of chest and abdominal pain continued. Four hours before death the patient sat bolt upright, screaming that he was blind. After thrashing around for a while, he became quiet and was found to be in shock. In response to treatment for shock, he rallied temporarily and evidence was obtained that he was not blind. Hemoglobin on the previous day had been 13.5 Gm.; now it was 4.5 Gm. He complained of abdominal pain; the abdominal wall was boardlike. His blood pressure, which had risen to 100, systolic, and 70, diastolic, soon fell again to an imperceptible level, and the patient expired.

Autopsy (Duke 4008).—The well-formed, undiseased heart weighed 380 grams. The foramen ovale was probe patent. The pulmonic end of the ductus arteriosus admitted a blunt probe for a distance of 1 mm.; the aortic end, 4 millimeters. The total length of this obliterated artery is 14 millimeters. Nowhere in the heart was there evidence of endocarditis or rheumatism. Measurements of significance regarding the heart and aorta are given in Table II. The branches of the aortic arch were situated in normal relation to one another. The aorta became abruptly narrowed in a funnel-like manner at the level of the left subclavian. From the stenosed ostium of the left subclavian, an intimal elevation or constricting band ran to the obliterated ductus arteriosus. The band occurred on the convex curvature of the arch, producing an externally perceptible indentation. The ostium of the subclavian was just proximal to one end of the band; the aortic ostium of the ductus arteriosus was just distal to the other end. Delicate vegetations were seen both on the caudal edge of the constriction band and in a number of places on the multilocular aneurysm which occurred on the right, posterior aspect of the aorta immediately below the ductus. The orifices of the right first to third and the left first intercostal arteries were involved in the aneurysm. The mouth of the 3 cm. deep aneurysm was 3 cm. in diameter. Several soft lymph nodes, about 1 to 2 cm. in diameter, and areolar tissue in the region of the tracheal carina were adherent to the outer wall of the aneurysm. Pus, a smear from which showed gram-positive cocci in chains, occurred in abscesses found between the aneurysm and the enlarged lymph nodes.

Other bacterial aneurysms were encountered in dissection of the abdomen. Three thousand cubic centimeters of partially clotted blood were found in the peritoneal cavity. The site of hemorrhage was a ruptured aneurysm of the superior mesenteric artery, 5 cm. from its origin. The intramesenteric hemorrhage from this saccular aneurysm, 2.5 cm. in diameter, consisted of a kidney-sized mass of clotted blood. An almond-shaped rupture of the parietal peritoneum, 5 by 3 cm. in size, at the root of the mesentery, accounted for the intraperitoneal hemorrhage from the same source. An aneurysm 4 cm. in diameter, with considerable laminated, organized thrombus, found near the head of the pancreas, was in the celiac axis (Fig. 3). Halfway between the head and tail of the pancreas, in the splenic artery, was an aneurysm, 1.5 cm. in diameter, filled with fresh thrombus. Six similar aneurysms were found in the intrahepatic ramifications of the hepatic artery. The iliac arteries were not dilated.

Old and new infarcts were found in the soft, flabby spleen (weight, 300 grams) and in the kidneys. The left kidney weighed 210 grams and had a double pelvis and two ureters (with separate orifices in the bladder). An accessory renal artery, originating two segments below the usual one, entered the left kidney at the lower pelvis. The right kidney weighed 150 grams. Both kidneys present the typical appearance of diffuse embolic glomerulonephritis.

Anatomic Diagnosis.—Coarctation of aorta, adult type; probe-patent foramen ovale. Aortic endarteritis (alpha streptococci) with aneurysm formation, involving right first to third and left first intercostal arteries; bacterial aneurysm of celiac axis, splenic, superior mesenteric, and intrahepatic portions of hepatic arteries. Rupture of aneurysm of superior mesenteric artery with retroperitoneal hemorrhage and secondary rupture of posterior parietal peritoneum into abdominal cavity; hemoperitoneum (3,000 c.c.). Embolic glomerulonephritis (alpha streptococci); acute splenic tumor; splenic and renal infarcts. Cardiac hypertrophy, left sided (380 grams); complete double pelvis and ureters and accessory renal artery, left.

Fig. 3.—Case 2. The aorta (A) is opened from behind. The outer surface of the cortex (with capsule removed) of the right kidney is shown on the right and the cut surface of the left kidney, on the left. Diffuse punctate hemorrhages are seen in both kidneys. Fresh and old (scars) infarcts (B) are visible. The double pelvis and ureters (C) and accessory artery (D) of the left kidney are illustrated. Between the upper pole of the right kidney and the aorta is an ovoid mass (E)—the celiac axis bacterial aneurysm, approximately 4 cm. in longest diameter.

DISCUSSION

The two cases of coarctation of the aorta were unusual because both had bacterial aortitis with aneurysm formation and embolic glomerulonephritis.

The diagnosis of coarctation and aortitis was not made during life in either case. The clinical picture of severe renal damage held the attention of those treating Case 1. The observation of one doctor, that the systolic blood pressure was 30 degrees higher in the arms, apparently was given little attention in view of the absence of radiological and auscultatory signs of collateral circulation. Renal damage was considered to be the cause of the hypertension. The relatively afebrile course did not direct attention to the bacteriemia responsible for the embolic glomerulonephritis.

In Case 2 the bacteriemia was recognized. The patient was thought to have bacterial endocarditis superimposed on rheumatic endocarditis or an un-

designated type of congenital cardiac malformation. Again the insignificant collateral circulation produced no radiological, and only inconstant auscultatory, signs which might have led to the recognition of the coarctation.

Very often one reads or hears that the adult type of aortic coarctation is easy to diagnose, but surely this is not really true. Many cases do not provide the classical criteria. Doubtless some of these cases, not examined at autopsy, are finally diagnosed clinically as examples of malignant hypertension or some other condition.

The clinical signs of coarctation are well known and will not be reviewed here. Abbott[1] found no definite correspondence between the grade of coarctation or the extent of collateral circulation and the physical signs. Signs are not most prominent in the cases which present the most marked alteration in the physical characteristics of the aorta or the collateral vessels. Rib notching, often first discernible near maturity, increases with the passage of years. This is secondary to an alteration which increases with age in the physical characteristics of the collateral circulation. Several factors may be responsible for the variation in degree of discernible change in collateral vessels: (1) inherent qualities of the vessels, (2) grade of coarctation and degree of hypertension in the aorta proximal to the constriction, and (3) other physical characteristics, habits and environment of the individual. There is not a definite correspondence between rib notching and auscultatory evidence of collateral circulation. It is conceivable that a minimal grade of physical alteration is essential to the production of auscultatory signs in the collateral circulation and that a higher grade alteration will, in addition, produce rib notching after sufficient time has passed. Although these signs of collateral circulation may be coexistent, either may exist alone. Autopsy evidence of collateral circulation was found by Abbott[1] in only 56 of 129 cases of the adult type (in the literature). Cases have been reported showing: (1) significant coarctation with physical signs of collateral circulation but no autopsy evidence of physical alteration of collateral vessels, (2) significant coarctation with neither clinical nor autopsy evidence of collateral circulation, and (3) significant coarctation with slight clinical and marked autopsy evidence of collateral circulation. The cases reported herein fall into the second category.

Aortic coarctation really presents a complicated engineering problem. Careful analysis of all the factors concerned might enable one to improve the correlation between clinical and autopsy data. That all factors have not always been considered is obvious from the discrepancies which exist—the frequent missed diagnoses. Reliable quantitative data are desirable. There ought to be a correlation between quantitative data on coarctation cases and normal cases of the same age, race, and sex. It is not possible easily to accumulate sufficient material to illustrate this concept adequately, but we hope the following observations will lead others to undertake the major task or to add observations which will aid some future worker in the final synthesis.

Cardiac auscultatory findings in coarctation (sysotlic murmur at the base with or without a diastolic component) may be due in part to the passage of blood through the constricted portion of the aorta and in part to the abnormal currents of blood set up proximal to the constriction. Many observers have described dilatation of the proximal portion of the aorta. The presence of such dilatation might conceivably aid in the production of a murmur at the base. It might also be a factor of significance in the degree of development of a collateral circulation. So far as we can determine, quantitative measurements and comparison with a set of standard measurements have never been

made to establish as a fact the theory that dilatation of the ascending aorta exists in cases of coarctation. It is obvious that comparison must be made with a set of standards in order to rule out causes of dilatation other than the coarctation (arteriosclerosis, syphilis, etc.). Additional factors affecting both the degree of dilatation of the ascending aorta and the physical signs in a case of coarctation include: grade of coarctation, cardiac hypertrophy, extent of collateral circulation, coincident malformations (bicuspid aortic valve of Case 1), and other conditions.

In the two cases reported, measurements were made at loci which may be taken as standard points for use in any other case. Ten similarly preserved normal hearts and aortas from other white males 19 to 23 years of age were measured at each of the positions indicated in Table II, and the means established thereby were used as normals in determining whether there is dilatation in the specimens of coarctation. Three independent measurements were taken to the nearest millimeter. The figures in the table are in centimeters and, with the exception of the first, represent circumference. It is evident that the number of specimens used is insufficient for the establishment of ideal normal measurements for this age period. Nevertheless, the following conclusions seem justifiable. There is left ventricular hypertrophy in both Case 1 and Case 2. There is dilatation of the innominate ostium in Case 2, dilatation of the subclavian ostium in Case 1, stenosis in Case 2, and narrowing of the aorta at the subclavian level in both. There is no real dilatation of the aorta proximal to the coarctation. In neither case is it feasible to measure the aortic circumference between the ductus and the fourth intercostal artery because of the presence there of the aneurysm. Hypoplasia of the aorta below this level seems evident in Case 1.

Abbott[2] found a statement about dilatation in 129 of 200 cases she reviewed. Hypoplasia was reported in 21, normality in 7, and dilatation in 101 cases. "The cause of the dilatation of the aorta in this situation is no doubt in part the increased intravascular tension that exists in the upper part of the body above the stenosis, under which the great branches of the arch also become dilated and also atheromatous. . . ."[2] Various other causes are considered contributory. Surely the pathogenesis will not be clearly understood until careful measurements have established the fact of dilatation and its relation to types and degrees of coarctation.

Bacterial Aneurysm.—Glomerulonephritis as a cause of death in coarctation of the aorta is not frequent. Probably in Case 1 an elevated blood pressure, caused by the coarctation, antedated the renal disease, while the glomerulonephritis was the result of long-standing bacteriemia from the bacterial aortitis. Death in uremia resulted from the extensive kidney impairment. A similar renal disease, but less extensive, occurred in Case 2. Death, in the second case, however, was from internal hemorrhage from one of the many bacterial aneurysms of arteries supplying the abdominal viscera. To be sure, the cause of death in both cases was intimately related to the aortitis. In both cases the aneurysm below the coarctation had progressed so far that it is fair to assume it might soon have ruptured. In Case 1 the esophageal mucosa comprised almost the entire remaining wall of the aneurysm.

In Case 2 four months before death a careful exploration of the mesentery at celiotomy showed no evidence of thrombosis. At autopsy, however, several large bacterial aneurysms with considerable thrombotic material were found. The small mass in the splenic artery might easily have been missed. If the aneurysm of the superior mesenteric artery had been present at that time, it

would have been discovered. Microscopically, the celiac axis aneurysm is the oldest. Had it been as large at the time of operation as it was at death, it could not have been missed. It is not unlikely that the symptoms which led to the celiotomy were produced by changes at this site, and that the mass later grew rapidly in size but was too small at that time to be palpated. Subsequently infected emboli broke off the thrombus in the celiac axis and lodged at numerous sites within the intrahepatic ramifications of the hepatic artery to produce the numerous bacterial aneurysms found there.

In Abbott's[2] 200 cases, bacterial endarteritis was present in 14. Death from rupture of the heart or aorta occurred in 40 cases; death from circulatory failure in 77 cases; and death from cerebral hemorrhage in 26 cases. Other causes of death were found in 43 cases.

From the literature as a whole are gleaned the cases outlined in Table III, in which an aortitis resulted in the formation of an aneurysm located just below the coarctation. Among these is the case of Kellogg and Biskind in which there was an additional bacterial aneurysm about 5 cm. from the origin of the superior mesenteric artery (compare with Case 2).

TABLE III. CASES OF COARCTATION WITH AORTIC ANEURYSM

AUTHOR	CASE	DEATH	ANEURYSM	COARCTATION	COMMENTS
1. Benecke	28 M	Cerebral hemorrhage	Directly below coarctation	Extreme stenosis beyond closed D.A.*	Glomerulonephritis
2. Evans Case 15	6 F	Rupture of aneurysm	Aortic end of closed D.A.	Moderate stenosis	Pneumococcus (?)
3. Focken Case 2	18 F	Septicemia	Directly below coarctation	Marked at closed D.A.	Glomerulonephritis streptococcus
4. Kellogg and Biskind	16 M	Cardiac failure	Directly below coarctation; superior mesenteric artery	Moderate. Slightly above patent D.A.	Aneurysm of superior mesenteric artery; streptococcus
5. Koletsky	38 M	Rupture of aneurysm	Directly below coarctation	Stenosis beyond D.A.	Acute glomerulonephritis
6. Libman, Abbott	12 F	Rupture of aneurysm into esophagus	Directly below coarctation perforating left bronchus	Moderate	Glomerulonephritis streptococcus
7. Reifenstein Case 2	10 M	Rupture of aneurysm into esophagus	Directly below coarctation, 3.5 by 5 cm. orifice	Marked 2.5 cm. —low subclavian	Pneumococcus
8. Smith and Hansmann	17 M	Rupture of aneurysm	1 cm. below coarctation, 6 cm. orifice	At closed D.A.	Streptococcus
9. Smith and Targett	9 M	Asphyxia cause by pressure of aneurysm	Directly below; 1.5 cm. orifice pressure on tracheal carina	Extreme at closed D.A.	Relation of aneurysm and esophagus like Case 1
10. Tillich	17 M	?	Directly below coarctation	Patent D.A. 4 mm. stenosis	Perforation of esophagus
11. Case 1	20 M	Uremia	Directly below coarctation	Marked	
12. Case 2	22 M	Intraperitoneal hemorrhage	Directly below coarctation	Moderate	

*D. A. = ductus arteriosus.

SUMMARY

Two cases of the adult type of aortic coarctation are presented. Anatomically these showed a moderate constriction and very little evidence of collateral circulation. Bacterial aortitis was present in both cases at the site of the coarc-

tation. In one case the bacterial infection was recognized and a congenital cardiac malformation was suspected. The other case was characterized by hypertension and advanced signs of renal damage so that blood cultures were not done and a cardiac malformation was not suspected. Quantitative measurements of the aorta and the mouths of the innominate and the left subclavian arteries in these cases and in a group of controls provide a means for evolving a more careful definition of the anatomic changes in coarctation. A better correlation between clinical and autopsy data is needed because many cases of coarctation are missed clinically.

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RUPTURE OF VENTRICULAR MYOCARDIUM

Report of Four Cases With Comments on Pathogenesis and on Clinical Significance of Possibility of Cardiac Rupture in Prognosis of Coronary Artery Disease

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SINCE coronary thrombosis became a popular clinical diagnosis, and the program of its treatment includes a minimum of six weeks' absolute rest in bed, cardiac rupture has loomed large in clinical thinking. The possibility of this complication in each case of myocardial infarction lends conviction to the argument which the physician advances in winning the cooperation of the patient and his attendants. The fear of cardiac rupture justifies sentencing the patient to being fed by spoon and to using a bedpan, even if there is a bathroom two steps away from his bed. How much of this fear is founded on fiction and how much on fact deserves serious reconsideration since, in the last twenty years, the diagnosis of coronary artery occlusion has become as popular as that of acute appendicitis, and the term coronary thrombosis has entered the vocabulary of laymen. The stories of these four cases of cardiac rupture may contribute something to the study of this problem.

CASE REPORTS

Case 1 (a-21-28 M. G. H.).—A woman, aged 78 years, sustained a Pott's fracture Jan. 15, 1921. On the twenty-third day of rest in bed she had cardiac pain; on the twenty-seventh day there was a second episode of severe cardiac pain, with shock and death half an hour after onset. All the coronary arteries were found to be widely patent, except the anterior descending branch of the left coronary artery, which was greatly stenosed by arteriosclerotic plaques and occluded by a thrombus; there was a myocardial infarct in the anterior ventricular wall with rupture in this area and hemopericardium.

This patient was a well-preserved, somewhat obese lady, 78 years of age. The only illness she remembered was a right otitis media at the age of 76 years. On Jan. 15, 1921, while doing housework, she sustained a left Pott's fracture and was admitted to the surgical ward of the Montreal General Hospital, attended by Dr. Pennoyer. The left lower extremity was placed in a box splint, and, eleven days later, a plaster cast was applied. On the twenty-third day of this illness, she complained of "severe epigastric pain, belching of gas and pain in the cardiac region; colour became pale and flesh clammy; pulse was thready." Morphine sulfate, 1/6 grain, soon relieved the pain and a soapsuds enema relieved the "gas." In the next four days she seemed to regain her usual health. On the twenty-seventh day of her stay in bed, at 7:30 P.M., she had "an attack of cardiac pain radiating to the shoulder and arm, along with some epigastric distress and belching of gas; very little dyspnoea. Pulse volume was full; rate, 110; rhythm, regular. Morphine sulphate, 1/6 gr., was given for pain. At 8:00 P.M. she had some dyspnoea and became worse: skin was white and cold; pulse thready and then imperceptible in a few minutes, and so she died of acute cardiac dilatation."*

At this time I was associated with the Department of Pathology and it was my lot to perform the autopsy in this case. The following is an abstract of the report:

Post-mortem examination revealed considerable obesity, extensive bands of fibrous adhesions in both pleurae, fibrous adhesions about the spleen and liver, and kidneys of normal

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*These quotations are from the intern's notes in the hospital record.

size. There was a moderate degree of arteriosclerotic changes in the kidneys. Cardiovascular system: the maximum diameter of the heart in situ was 14 cm.; the pericardium was tensely distended, containing 200 c.c. of fluid blood and about 100 c.c. of blood clot. An abundance of epicardial fat was noted. The heart weight was 270 grams. On the anterior surface of the left ventricle, 5 cm. above the cardiac apex and just to the left of the interventricular groove, there was a transverse laceration 1.5 cm. wide (Fig. 1). A probe passed through this readily into the left ventricular cavity. There was no evidence of enlargement or hypertrophy. Slight arteriosclerosis of the aorta, mainly in its descending portion, was observed. The coronary artery orifices were patent and of normal size. The right coronary artery and its branches presented evidence of a slight degree of arteriosclerosis without stenosis. The left main coronary artery and its circumflex branch were similar to the right coronary artery. The anterior descending branch of the left coronary artery was greatly stenosed by large arteriosclerotic plaques, and, in the proximal third, it was occluded by an adherent recent thrombus.

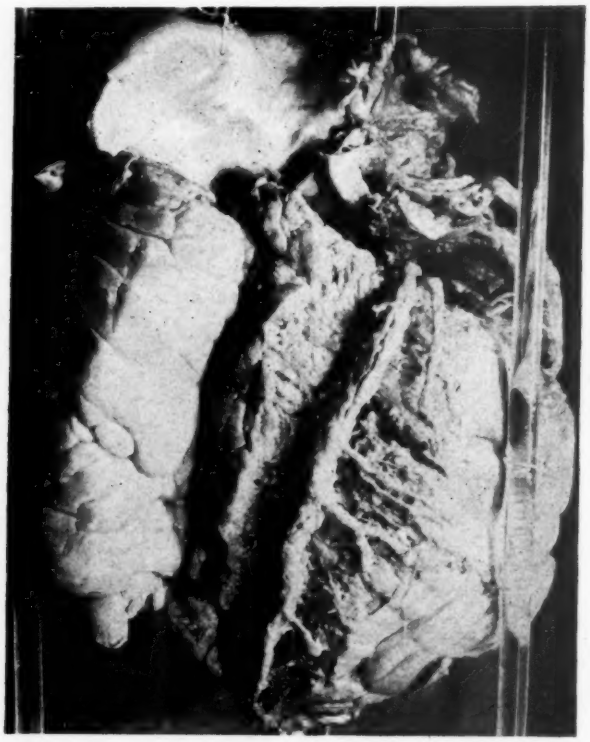

Fig. 1.—Case 1. Anterior surface of ventricles: anterior descending branch of left coronary artery and some of its branches exposed. Note transverse tear in left ventricle. When opened longitudinally, the artery was found markedly stenosed by arteriosclerotic plaques in its whole length and occluded by a thrombus lying in its proximal third.

The smaller branches of this artery were also sclerosed. Microscopic examination in the region of the cardiac rupture revealed necrosis of muscle fibers, infiltration with masses of red blood cells, and also some inflammatory reaction manifested by the presence of leucocytes. Microscopic section of the myocardium of the left ventricle beyond the area of infarction revealed fatty infiltration of moderate degree and some increase in the width of the fibrous interstitial tissue.

Perhaps the clinical history is incomplete, but it has long been known that extensive arteriosclerotic disease of coronary arteries may exist for many years in some people without causing any symptoms. This patient illustrates this and also the fact that a myocardial infarct was established as a result of thrombosis of the only coronary artery that was affected by arteriosclerosis to a significant degree. Thus, in spite of ideal conditions for the development of collateral circulation, which would minimize the effect of sudden occlusion, infarction developed, and rupture of the myocardium occurred within the infarct.

Nor was bodily exertion an element of etiology for either the thrombotic occlusion or the myocardial rupture. The entire cardiac episode evolved while the patient was at rest in bed for the treatment of a Pott's fracture. The normal size of the heart supports the view that this patient had a normal or relatively low blood pressure. Thus the rupture must be explained mainly by processes of disease in the myocardium. On the fourth day after occlusion of the coronary artery, the infarct contained areas of myocardial degeneration of various sizes and shapes. Though the blood pressure was within normal limits, the thick ventricular wall was ruptured through the infarct. Small tears probably occur very commonly in myocardial infarcts, but in this instance the plane in which the tear was initiated led to its extension, until it reached the epicardial surface. The last half hour of the patient's life was most likely the period in which the epicardium was torn and the cardiac tamponade developed.

CASE 2 (J. G. H. A44-838).—A man, aged 61 years, experienced three episodes of myocardial infarction in thirty months. The first two were untreated at the onset and subsequently treated with rest in bed; the third was recognized at the onset and treated with strong sedatives and absolute rest in bed. Rupture of the myocardium occurred, followed by death on the fifth day of the third episode.

First Episode.—This man was in good health until the age of 59 years, when, in July, 1941, he began to have pain in the left shoulder and profuse sweating, which wakened him from sleep almost every night. On Nov. 21, 1941, at 2:00 A.M. he woke feeling severe "soreness" under the lower two-thirds of the sternum and in the left shoulder and arm. He had some nausea but could not vomit. He perspired profusely. At 6:00 A.M. Dr. Mingie saw him, diagnosed coronary thrombosis, and ordered rest in bed for several weeks. However, the patient ignored this advice and, on the following day, returned to his work as an executive in a factory. On November 23, he shovelled snow to clear his garage driveway. He felt he had a mild cold on November 24, and remained at home that day and the next. He first consulted me on November 26, not because he felt sick, but to placate his family. He had not had any previous illness. In his business affairs he had had many ups and downs, and, since 1940, they had been in a serious state of depression.

Physical examination revealed a rather slender, agile man, 5 feet, 5 inches, in height and weighing 140 pounds; his complexion was pale. There was no anemia; the liver edge could be felt 6 cm. below the costal border on deep inspiration; and the lung signs were normal. An orthodiagram of the heart revealed: aortic arch, 4.5 cm.; right border, 5 cm.; left border, 7.8 cm.; transverse diameter of chest, 27 cm.; and aorta, somewhat elongated. The heart sounds were normal except for an amphoric quality of the second sound at the apex. A faint systolic murmur between the first and second sounds was heard all over the precordium, and a very faint diastolic murmur immediately after the second sound at the left border of the sternum between the fourth and sixth costal cartilages was also observed. The blood pressure was 106/66 (Fig. 2); neurological signs, normal; fundi, moderate tortuosity of retinal arteries; urine, specific gravity, 1.020 (no sugar or albumin); blood Wassermann, negative. An electrocardiogram (Fig. 3*A*) revealed no evidence of recent or old myocardial infarct and a left axis deviation, suggestive of some left ventricular enlargement. He remained at home in bed (with bathroom privileges) during the next six days, and then entered the Western Division of the Montreal General Hospital for further investigation. Studies made in the course of fifteen days revealed no fever; four white cell counts between 6,400 and 7,900; four sedimentation velocity determinations, 0.5 to 0.65 (normal 0.08 to 0.38 mm. per minute); and seven electrocardiograms revealed slight variations in amplitude of positive T in Leads I and II, more marked variations from positive to negative T in Lead III and a normal CF_2 (Fig. 3).

Diagnosis: arteriosclerotic (and probably hypertensive) heart disease; coronary arteriosclerosis with stenosis; occlusion of a coronary artery with myocardial infarction; and moderate left ventricular enlargement. He remained at home in bed (with bathroom privileges) for another six weeks, then convalesced for several weeks. He frequently had pain in the right shoulder on movement of this joint, usually before changes in the weather. Physical examination on June 25, 1942, revealed no new feature, except that the blood pressure was 150/80; the electrocardiogram was similar to the previous record. During the next year and one-half he rarely had substernal discomfort; if it occurred on hurried walking, it

was quickly relieved by rest or, if initiated by excitement, by moving away from the scene. He did not require nitroglycerin and took no other medication. On July 23, 1943, an electrocardiogram recorded by Dr. H. Shister was similar to the record of June, 1942.

Second Episode.—On Dec. 19, 1943, at 2:00 A.M. the patient was wakened from sleep with pain under the mid-sternum and in the left arm. His forehead was "wet and cold." A nitroglycerin tablet taken on wakening seemed to produce relief in a "few" minutes ("perhaps three minutes"); the ache in the left arm was last to disappear. The patient continued at work as usual and consulted me for a "periodic check-up" on Dec. 22, 1943. His general appearance was good; new features as compared with observations of June, 1942, were: diminution in loudness of the first heart sound; blood pressure, 160/98; and a grossly abnormal electrocardiogram, showing inversion of T_1, almost isoelectric T_2, inversion of T in Leads CF_2 and CF_4. This brief cardiac pain did not justify the diagnosis of coronary artery occlusion, rather did it suggest prodromal symptoms, perhaps due to hemorrhage into an arteriosclerotic plaque causing stenosis of a large coronary artery. Rest in bed (with bathroom privileges) for a month was prescribed. On Jan. 18, 1944, he reported he had had no discomfort during this month. His blood pressure was 130/80; the first sound appeared louder than on Dec. 22, 1943, but less loud than in June, 1942; an unusually prominent and forceful pulsation in the fifth left intercostal space near the sternum suggested aneurysm of the anterior ventricular wall; and the electrocardiogram was similar to that of Dec. 22, 1943. It was thought that the new infarct in the anterior ventricular wall had occurred "painlessly" at some time between July and Dec. 22, 1943. He was permitted to resume light activities in his business and was free from symptoms for one month.

Third Episode.—On Feb. 17, 1944, he slept soundly from 10:00 P.M. to 4:00 A.M., when he awoke with severe pain in the interscapular region, marked sweating, and some substernal aching. Nitroglycerin did not relieve this pain. He waited until 7:00 A.M. to call me and was given morphine sulfate, ¼ grain, hypodermically at 7:30 A.M. by Dr. Golfman. This relieved the pain to a considerable degree and made him drowsy and nauseated. When I saw him at 10:00 A.M. he appeared paler and more sallow of complexion than usual; he had some aching under the sternum and was drowsy. His blood pressure was 120/90, but the brachial artery sounds were faint, suggesting reduced volume of cardiac output per beat. Faint heart sounds and a blowing systolic murmur, loudest at the apex and at the left border of the sternum near the fourth intercostal space, suggestive of mitral insufficiency, were new features. An electrocardiogram showed gross changes indicative of recent ventricular infarct. The systolic murmur suggested infarction and perhaps tearing of a papillary muscle in the left ventricle. During the day of February 17 he wakened frequently with moderately severe pain, interscapular and substernal, of several minutes to a half hour in duration until he dozed off again. He was given ¼ grain of morphine sulfate at 10:00 P.M. and slept well after 11:00 P.M. On February 18 he was free from pain or dyspnea and at 10:00 P.M. his blood pressure was 110/84; the heart sounds and the murmur were almost the same as on February 17. On February 19, at about 8:00 A.M., he began to have dyspnea; at 9:30 A.M. moist râles were heard at both bases by Dr. Golfman, who, however, found no indication for morphine and prescribed ¼ grain of codeine phosphate as a sedative. At about 3:00 P.M. he became acutely and severely dyspneic, very restless, and apprehensive. At 4:45 P.M., I observed marked cyanosis of hands and feet; coldness of the skin; continual moderate sweating; marked orthopnea; rapid, rather shallow respiration; marked anxiety; blood pressure, 104/90; and very faint brachial artery sounds. Auscultation of the heart revealed a rapid rate (140) and faint heart sounds, almost inaudible at the apex and the base, but the chief feature was a loud systolic murmur with a new, "whee jee wee"-like quality, loudest at the right border of the sternum. In thinking of how to describe this murmur, I thought it sounded like the noise produced in squeezing raw meat. This led to the thought that the new developments in the clinical picture might be due to rupture of the myocardium. The murmur was not loud enough to justify placing the site of the rupture in the interventricular septum but was suggestive of rupture of the ventricular wall with a slow leak through the almost intact pericardium. Electrocardiograms taken on February 18 and 19 suggested anterior wall infarction, and reduction in the amplitude of QRS was compatible with pericardial effusion. Satisfactory percussion revealed no change in the heart size to confirm the suspicion of hemopericardium. The absence of a diastolic phase of the murmur suggested that the peculiar quality of the murmur did not represent a friction murmur, but this possibility could not be ruled out entirely. At 6:00 P.M. he was admitted to the Jewish General Hospital. At 11:00 P.M. only a faint systolic murmur at the left border of the sternum could be detected, and our opinion favored pericarditis as the cause of the unusual murmur that was heard earlier.

The systolic blood pressure was now only 30; the brachial artery sounds were extremely faint, and the radial pulse was extremely small. Cyanosis of the extremities persisted, although the patient had been in an oxygen tent for about five hours. The suspicion of ventricular rupture inhibited me from giving blood plasma for the treatment of shock. The next day, about twenty-eight hours after the onset of this grave phase of the illness (with anuria present

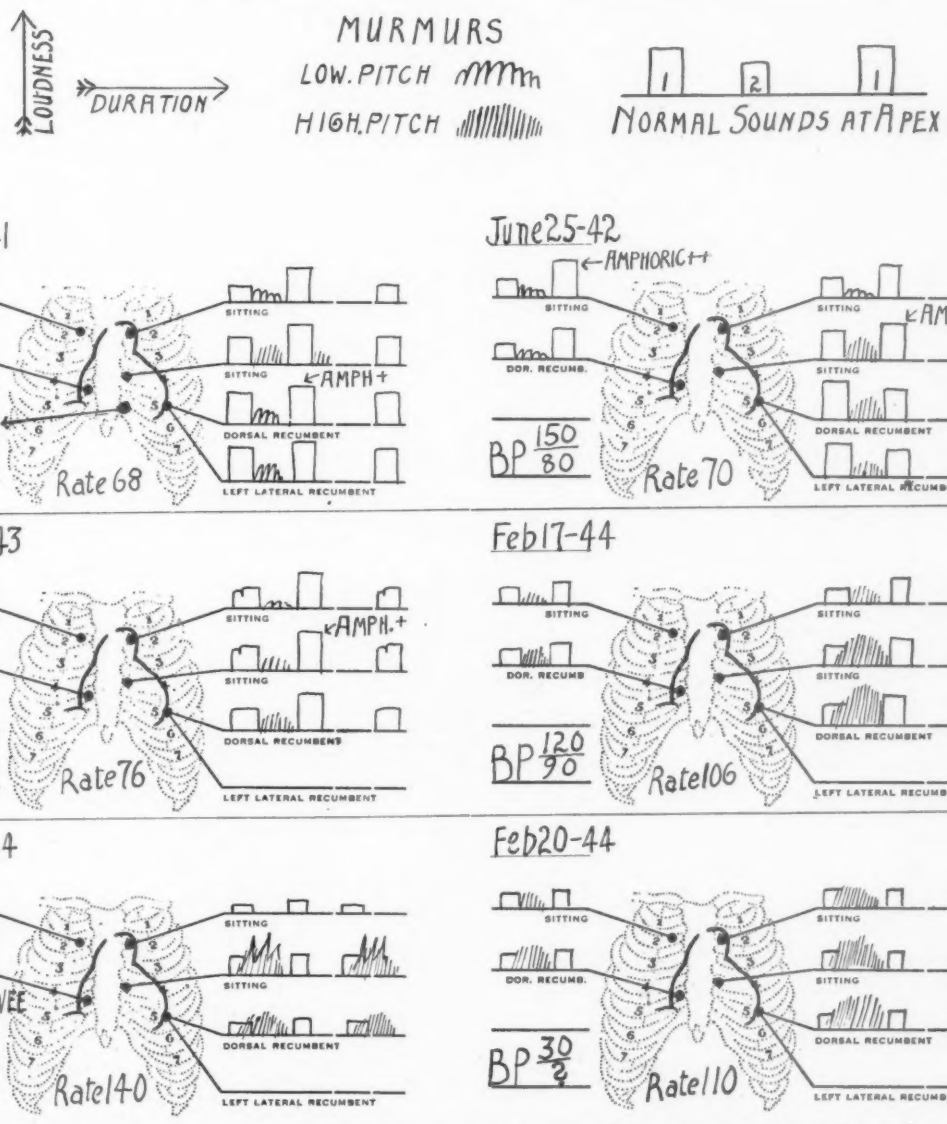

Fig. 2.—Case 2. Heart sounds and murmurs. Nov. 26, 1941: Amphoric second sound at apex suggests a large gas bubble in stomach; faint aortic insufficiency murmur was heard only on this day and suggests transient aortic insufficiency of slight degree or pericardial friction murmur. Systolic murmur not loud or long enough to be evidence of valvular disease.

June 25, 1942: Amphoric second sound a new feature, suggests arteriosclerosis with some dilatation of ascending aorta.

Dec. 22, 1943: Only minor variations observed until this date, when the first sound was much less loud than formerly with no change in the second sound. Electrocardiogram revealed evidence of recent myocardial infarct near cardiac apex in anterior wall.

Feb. 17, 1944: Seven hours after onset of third episode of myocardial infarction during which rupture of myocardium occurred. Loud systolic murmur indicative of mitral insufficiency suggests diagnosis of torn papillary muscle.

Feb. 19, 1944: Heart sounds very faint, heard only during sustained expiration, but peculiar "whee-jee-wee" murmur together with systolic murmur of mitral insufficiency was readily audible. This peculiar murmur suggested rupture of ventricular wall, but was probably a pericardial friction sound.

Feb. 20, 1944: At one time on this day (twelve hours before death) the systolic murmur of mitral insufficiency was quite loud, although blood pressure was very low; later the murmur and heart sounds became very faint.

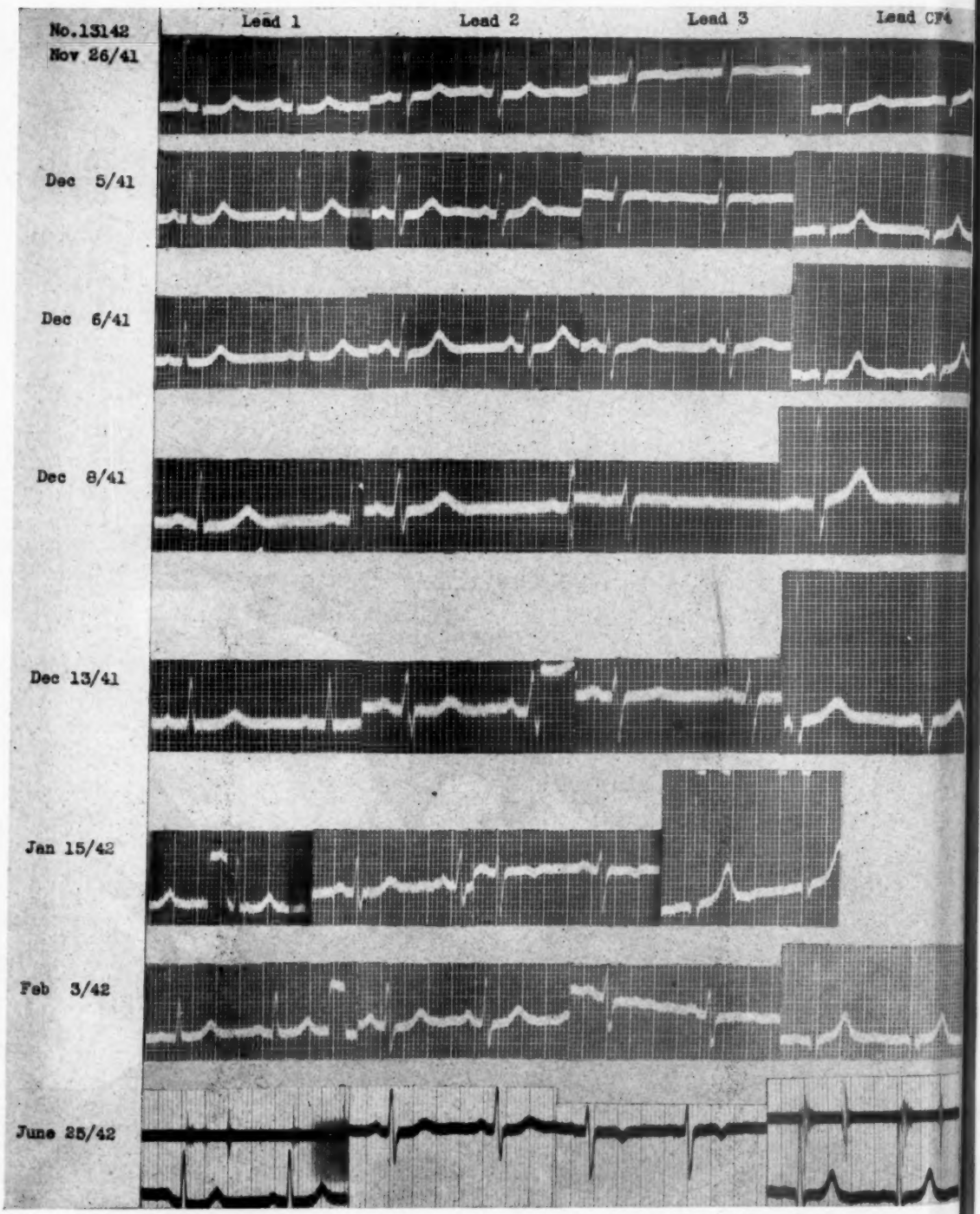

Fig. 3A.—Case 2. The six records made between Nov. 26, 1941, and Jan. 15, 1942, were selected from eight made in this period. They show slight variations in the S-T segment of Leads I and II, changes in T of Lead III from positive to negative and variations in amplitude of T in CF_4. These minor abnormalities were related to healing and fibrosis of an infarct in the central portion of the interventricular septum. The records of Feb. 3, 1942, and June 25, 1942, show very slight changes in T of Lead III.

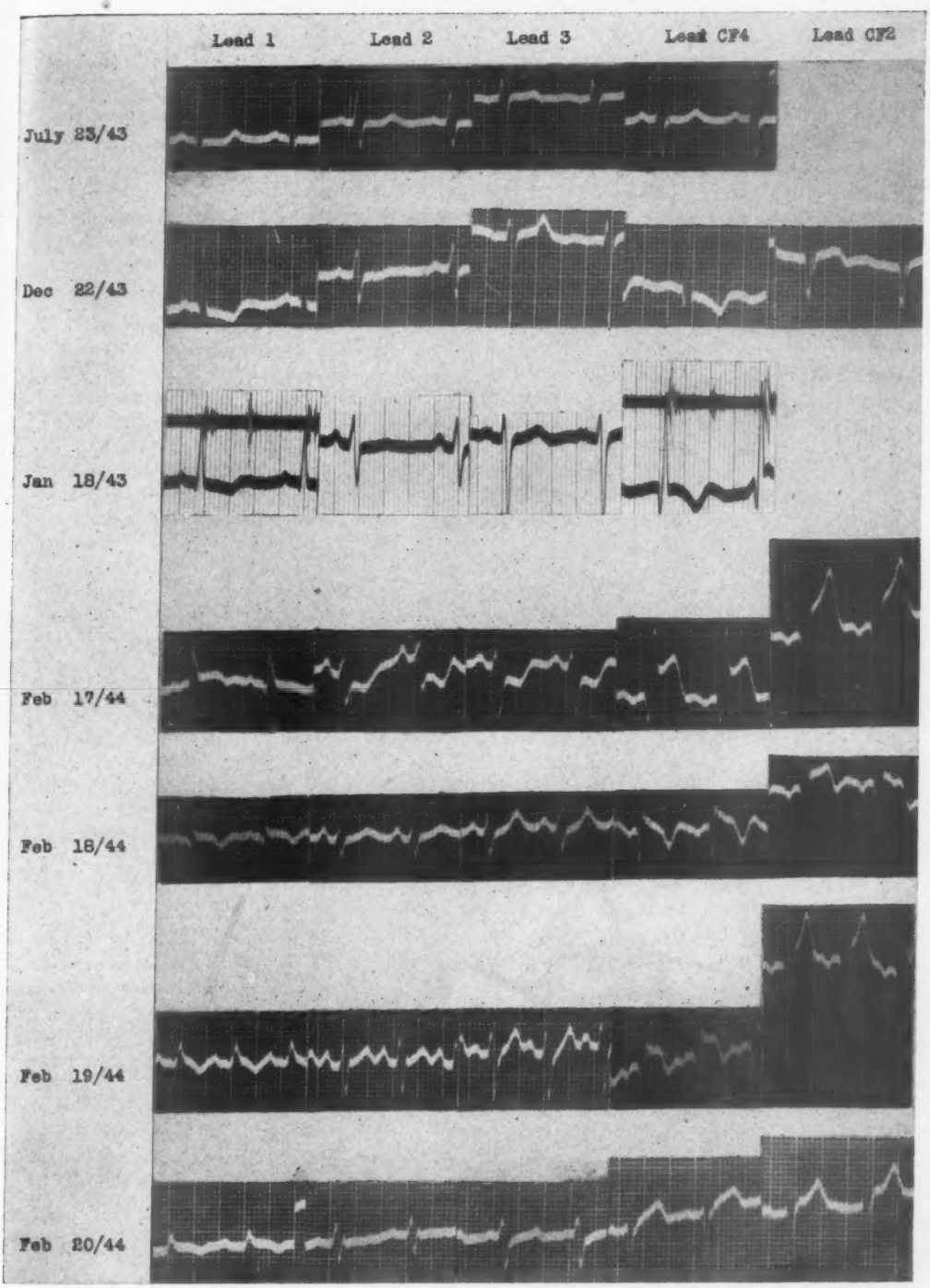

Fig. 3*B*.—Case 2. The record of July 23, 1943, is similar to that of Dec. 6, 1941, with positive T waves in Lead III. The first gross abnormalities appear in the records of Dec. 22, 1943, and Jan. 18, 1944. They are related to infarction of the anterior wall of left ventricle with aneurysmal dilatation near the apex. Note diphasic T in Lead I, low voltage of T in Lead II, high T in lead III, and inverted T in CF_4 and CF_2. The amplitude of R in Lead I and S in Lead III have increased, suggesting left ventricular enlargement. In the record of Jan. 18, 1944, the phonocardiogram recorded simultaneously with Lead CF_4 represents the heart sounds over the region of the fourth intercostal space, near the sternum; an auricular sound of low amplitude was recorded on this day, which was not audible during ordinary auscultation and was not recorded in June, 1942. This new feature probably represents the effect of thinning of the left ventricular wall near the apex, following infarction about a month or more previously.

The last four records represent the effects of thrombosis of the left circumflex branch of the left coronary artery with infarction in the left ventricle at its left margin and posteriorly, tearing of the anterior papillary muscle near its base, rupture of the left ventricle and hemopericardium. There is no specific feature to suggest rupture of the myocardium. Changes from negative to positive T in Lead CF_4 point to involvement of the posterior ventricular wall.

during all this time) persistence of the blood pressure at about 30 mm. led to the decision that 500 c.c. of a 10 per cent glucose solution should be given and should be followed by plasma until the blood pressure would rise, or until, as expected, the patient would die. Percussion again failed to reveal any sign of pericardial effusion, and there was no pericardial friction murmur, but only the blowing systolic murmur which suggested rupture of a papillary muscle causing mitral insufficiency. He remained mentally clear until about six hours before his death, which occurred at 4:00 A.M., Feb. 21, 1944, ninety-six hours after the onset of the final illness and thirty-seven hours after the beginning of the terminal grave phase. Pulmonary edema and unconsciousness developed gradually in the last six hours. The autopsy was performed by Dr. M. Simon and the following is an abstract of the report.

The right pleural cavity contained 300 c.c., and the left 200 c.c., of straw-colored fluid with a specific gravity of 1.010. There was a moderate degree of pulmonary edema; the abdominal viscera showed evidence of a mild degree of chronic passive hyperemia. The heart (Fig. 4) was enlarged (510 grams); the pericardium appeared somewhat tense and, on being opened, revealed a thin layer of dark red blood covering the whole surface of the heart; a thin, sticky, fibrinous exudate bound the pericardial surfaces, particularly over the anterior aspect of the heart. A poorly defined bulge about 3 cm. in diameter was found near the apex of the left ventricle; on the anterior surface of the left margin of the left ventricle, about 6 cm. from the apex, a mottled yellow and red depression, about 4 mm. in diameter, was present; a fine probe passed through this depression into the left ventricular cavity leading to the base of the anterior papillary muscles. This track lay in a recent infarct. The anterior left ventricular wall for a distance of about 5 cm. above the apex was yellowish red, mottled, and friable. Section through the interventricular septum revealed the appearance of extensive fibrosis, evidence of an old, healed infarction. There was a mural thrombus at the bulging area near the left ventricular apex and a smaller (2 cm. in diameter) thrombus in the left auricular appendage. The valves revealed no abnormalities. The left circumflex artery was markedly sclerosed and, beginning 2 cm. from its origin, there was an adherent red thrombus which extended into and occluded several of its medium-sized branches, which lay in the area of recent infarction. The anterior descending ramus of the left coronary artery was markedly stenosed by arteriosclerotic plaques. At a point 1 cm. from its origin, section revealed only a pin point eccentric lumen. Below this point sections revealed no gross evidence of any lumen. The right coronary artery was less extensively sclerosed, but at a point 2 cm. from its origin, there was a thick arteriosclerotic plaque, reducing the lumen to about one-third of the diameter of the artery. The aorta revealed arteriosclerosis, most marked in the lower abdominal region and extending into the iliac arteries.

Microscopic examination of a section of the left anterior descending branch of the left coronary artery showed extensive calcification of the media and numerous atheromatous plaques containing acicular slits. About one of the larger plaques, numerous phagocytes filled with golden-brown, granular pigment were noted. There was also evidence suggesting canalization of an old thrombus. Section through the left circumflex branch of the left coronary artery revealed a markedly thickened, partially calcified wall containing a large atheromatous plaque. The lumen was completely occluded by a laminated recent thrombus. Section through the left ventricle at the site of the perforation showed extensive necrosis of the myocardium, interstitial hemorrhages and a diffuse infiltration by large numbers of polymorphonuclear leucocytes. Between the columnae carneae a large laminated recent thrombus was present. At some distance from the area of recent infarction focal areas of fibrosis were seen in the myocardium.

Correlation of clinical observations and thoughts with what was found at autopsy suggests that the peculiar "whee-jee-wee" systolic murmur (Fig. 2) was more likely due to pericardial fibrin deposits from blood which had oozed slowly into the pericardial cavity than to blood squeezing through the track of ventricular rupture. This murmur did not bear any resemblance to that described by Reznikoff[9] in a case of a ruptured anterior wall of the left ventricle, following coronary thrombosis. The murmur was heard best near the fourth and fifth right costal cartilages over the right auricle and the right border of the right ventricle; the pericardial end of the ruptured ventricle was far to the left, on the left cardiac border in the vicinity of the fourth left rib, about 7 cm. from the mid-sternal line. Only by imagining a peculiar effect of the stream of

ejected blood coming through the pericardium, so that the murmur was produced near the right border of the heart, instead of over the area of the rupture, could one relate the murmur to the rupture. This must be considered an unlikely possibility. Thus, the ante-mortem diagnosis of cardiac rupture was made in part on false premises. Moreover, the site of the rupture was not as predicted, for it was thought that it would involve the aneurysmal dilatation which seemed to be in the anterior ventricular wall to the right of the cardiac apex. The aneurysmal dilatation near the cardiac apex was intact and occupied by an old, adherent laminated thrombus.

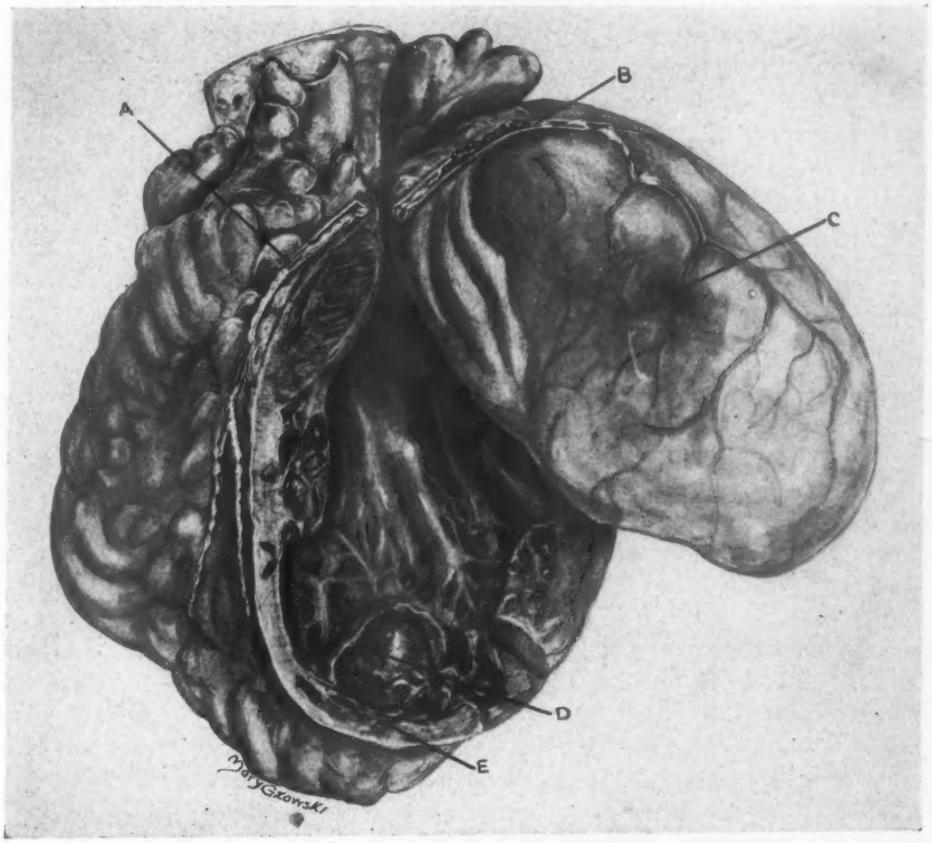

Fig. 4.—Case 2. *A*, Stenosed anterior descending branch of the left coronary artery. *B*, Thrombus in circumflex branch of the left coronary artery. *C*, Site of rupture. *D*, Mural thrombus. *E*, Aneurysm of anterior wall of left ventricle.

It is most likely that tearing of the myocardium began soon after occlusion of the left circumflex coronary artery and that the initial tears involved the base of the left anterior papillary muscle, resulting in some mitral insufficiency which revealed itself by the loud, blowing, systolic murmur. Some degree of shock was present from the beginning of this episode, but the severe degree which began about thirty-seven hours before death could have been coincident with progressive extension of the track of tearing until it reached the pericardium, when acute dyspnea, chest pain, marked fall in blood pressure, cold extremities, etc., set in. The thin layer of bloody fluid in the pericardium must have accumulated slowly in this period of about thirty-seven hours and was not enough to cause cardiac tamponade. It appears most probable that death was a direct sequence of the state of shock rather than a direct result of the cardiac rupture.

The state of shock was initiated primarily by thrombotic occlusion of the left circumflex coronary artery and probably aggravated by the process of myocardial tearing to the point of rupture through the pericardium.

The marked fibrosis in the interventricular septum probably represents the site of myocardial infarction during the first illness in November, 1941. It is of interest that the electrocardiograms related to this revealed only minor abnormalities of T waves in Lead III and no notching or prolongation of QRS (Fig. 3). The infarction near the apex of the left ventricle, resulting in a slight aneurysmal dilatation, occurred almost painlessly at some time between July and Dec. 22, 1943. The attack of cardiac pain, which woke him from sleep on Dec. 19, 1943, and which lasted about three minutes and was relieved by nitroglycerin, did not suggest coronary artery occlusion with myocardial infarction. It was interpreted as evidence of considerable arteriosclerotic stenosis of one of the larger coronary arteries. A small hemorrhage into an arteriosclerotic plaque was visualized, and a program of rest in bed for several weeks was advised, because this event was looked upon as possibly prodromal to coronary artery occlusion. Microscopic examination of the ventricular muscle in this region revealed evidence of active disease, indicating that the infarct was relatively recent. It now appears most likely that the brief episode of pain did represent occlusion of the considerably stenosed anterior descending branch of the left coronary artery. Thus, about two months after this had occurred, fibrosis of the infarct was not yet complete. This slow healing may in part account for the development of some aneurysmal dilatation which was detected clinically a month after the infarct was initiated.

The anatomic findings do not provide an adequate explanation for some features of the clinical picture. There is the fact that the earliest symptoms of impaired coronary circulation occurred at night, wakening the patient from sleep, and consisted of transitory left shoulder pain with profuse sweating. Much later and only after the first episode of coronary artery occlusion, did he begin to suffer from the more common symptom-complex of substernal and left-arm pain on hurried walking, or as a result of acute excitement. Also, the first attack was not associated with the development of shock, the second was almost symptomless, and the third, the only one that was treated in orthodox fashion from the beginning, led to shock and was complicated by rupture of the ventricle, terminating fatally. These problems are mentioned in order to indicate that knowledge of the morphology of the heart and blood vessels does not solve them; the correct answers must await a fuller knowledge of pathologic physiology. The initiation of cardiac pain, by acute excitement such as anxiety, or by a sense of hurry as when the individual fears he may be late in reaching his destination as he sits comfortably in a vehicle, are familiar psychosomatic phenomena. It has been shown that in the dog[1] the vagus nerve acts as a vasoconstrictor for the coronary arteries, and that central or reflex increase in tone of the vagus center causes reduction in the quantity of blood flow through coronary circulation. These facts lead one to search for the psychic phenomena which may occur during sleep and which would increase vagus tone. Such knowledge might account for the central and reflex type of coronary vasoconstriction. Recently, Waugh and Ruddick[12] have reported that during uncomplicated rest in bed there is an increase in coagulability of blood. This fact may eventually be associated with others, which might explain the occurrence of coronary artery thrombosis during absolute rest or during sleep, as in three of these four cases.

CASE 3 (J. G. H. 23729).—A woman, aged 67 years, was admitted for investigation of intestinal hemorrhage and anemia. Carcinoma of the cecum was found. Acute weakness and chest pain, lasting about an hour, occurred six days before sudden death. Autopsy revealed embolus of vegetation from the mitral valve to the left circumflex branch of the left coronary artery and rupture of the left ventricle.

A small, pale, poorly nourished woman of 67 years, weighing about 80 pounds, had seen blood in her stools occasionally for some years and more frequently for some months before admission. She had had arthritic aches and pains for many years, but no cardiac symptoms. Physical examination revealed slight cardiac enlargement and a blowing systolic murmur, loudest at the apex, partially masking the latter half of the first sound and suggestive of mitral insufficiency. Her blood pressure was 150/80. The cecum appeared to be rather broad; large external and internal hemorrhoids were observed; gastric analysis was normal. An x-ray examination suggested a lesion in the lower pole of the cecum and calcification in the aortic valve. Hemogram: 2.9 million red cells; 39 per cent hemoglobin; 9,400 white cells; and 83 per cent polymorphonuclear. Blood Wassermann was negative. Fasting blood sugar was 108 mg. per cent; nonprotein nitrogen was 24 mg. per cent. On July 10, 1940 (the sixth day in the hospital), at 8:30 A.M. the patient suddenly felt very weak. She had pain in the left breast region; the pulse was weak, rate, 42. Some pain persisted for about an hour and she had weakness during the whole day. Her blood pressure was 136/70 at 10:00 A.M. She had a barium enema in the afternoon. A transfusion of 300 c.c. of blood was given the following day. The stools contained large amounts of dark red blood. During the next five days she had no pain in the chest but was weak and drowsy until sudden death occurred at 10:30 A.M., about a half-hour after an effectual enema that had not caused any discomfort. The patient had been constantly in bed while in the hospital for twelve days.

Clinical Diagnosis: Carcinoma of the cecum; severe hypochromic anemia; large hemorrhoids; general arteriosclerosis; moderate cardiac enlargement; mitral insufficiency; and calcification of the aortic valve. The autopsy was performed by Dr. M. Simon, and the following is an abstract of his report.

Well differentiated adenocarcinoma of the cecum was present near the ileocecal valve; there were metastases to the peritoneum, spleen, omentum, and lymph nodes at the porta hepatis. Pulmonary emphysema and internal and external hemorrhoids were observed. Cardiovascular system: the pericardium contained about 300 c.c. of pale, watery, blood-tinged fluid; the heart was of average size; the epicardium was normal; and a small amount of subepicardial fat was present. At about the middle of the posterior wall of the left ventricle a linear tear, 12 mm. long, was observed; a probe passed through this tear into the left ventricle. The endocardium of the left auricle was somewhat opaque and wrinkled; the mitral valve appeared slightly thickened and there was slight fusion of the leaflets: just above the line of closure, on the auricular surface of both leaflets, there were four small pinkish-yellow vegetations (3 to 4 mm. in diameter). The endocardial end of the cardiac rupture was 3 mm. in diameter, situated behind the posterior leaflet of the mitral valve, nearer the base than the apex of the left ventricle. The cut surface of the myocardium in the vicinity of the tear showed slight reddish-yellow mottling. There was a slight fusion of the left coronary and the noncoronary cusps at the aortic valve for a distance of about 3 mm. at the commissure. The circumflex branch of the left coronary artery was somewhat larger than normal. At a point about 3 cm. from its origin, and where it gives off a branch which goes to the region of the myocardial tear, there was a pinkish-yellow, adherent mass of material which resembled the mitral valve vegetations and completely occluded the arterial lumen. The remainder of the coronary arteries revealed slight to moderate degree of arteriosclerosis. Microscopic examination of the embolus and of the mitral valve vegetations showed them to be similar, pink-staining amorphous material with focal collections of polymorphonuclear leucocytes and strands of fibrin and no bacteria. In the region of the tear, the myocardium revealed only slight hemorrhage along its edges and extensive replacement of muscle fibers by granulation tissue, containing fibroblasts and histiocytes, many containing golden-brown granular pigment. At some distance from the margin of the tear, there were foci of myocardial necrosis containing polymorphonuclear leucocytes. At only one point near the edge of the tear, the connective tissue about a thick-walled artery contained histiocytes, lymphocytes, and occasional polymorphonuclear leucocytes. This resembled an Aschoff body. Elsewhere in the myocardium no Aschoff bodies were found.

The significance of the acute episode of weakness, bradycardia, and pain in the left breast region, which occurred six days before death, was not recog-

nized. It was considered as part of the clinical picture of arthritic pain in an emaciated old lady, suffering also from marked anemia, associated with carcinoma of the cecum. If electrocardiograms had been recorded in the interval of six days before death, the diagnosis of myocardial infarction probably due to coronary thrombosis might have been made. The sudden death might have been associated with this diagnosis. Death occurred within about two minutes after the patient suddenly appeared gravely ill with labored breathing and a very small, thready pulse. There was no indication of severe pain. The epicardial opening was 12 mm. and the endocardial, 3 mm. in length. This suggests that cardiac tamponade developed rapidly. Except for the x-ray examination of the lower bowel, which was carried out in the dorsal recumbent posture, this patient had not been disturbed by any special studies and remained constantly in bed. This did not prevent evolution of infarction and rupture of the myocardium. Moreover, there was no hypertension. If the myocardial infarct had been recognized, sudden death on the sixth day might have justified considering the possibility of cardiac rupture as the cause of death, but other possibilities such as ventricular fibrillation, occlusion of a large coronary artery, etc., also existed.

CASE 4 (M. G. H. A-44-41).—A man, aged 61 years, had hypertension for more than three years. Twenty days before death he began to have cardiac pain only on walking outdoors. For eleven hours before death he had severe cardiac pain. Autopsy revealed rupture of the anterior wall, involving both ventricles and the interventricular septum and probable rupture of the coronary artery.

This man was a machinist. He had had pneumonia at the age of 27 years. On April 17, 1941, at the age of 58 years, he experienced numbness and weakness of his left hand for several hours, and his blood pressure was 172/90. These symptoms lasted only one day. Blood Wassermann reaction was negative. On Jan. 25, 1944, he began to have pain across both shoulders posteriorly and under the lower front of the chest after walking outdoors for a few minutes. This came on more readily soon after meals than when the stomach was empty; stopping to rest for a minute or two brought relief. The patient experienced no discomfort indoors, either at work or rest. Physical examination, Feb. 8, 1944, he appeared younger than 61 years and could pass for 50; his weight was 152 pounds, and his height, 5 feet, 5 inches. Neurological signs were normal; the liver edge was felt 4 cm. below the costal border on deep inspiration; and the lung signs were normal. A forceful cardiac apex impulse in the fifth left intercostal space, 9 cm. from the midsternal line, suggested some cardiac enlargement. The second heart sound had an amphoric quality at the apical and tricuspid areas only; no other abnormalities of heart sound were heard. Blood pressure was 210/110. An electrocardiogram showed normal rhythm; rate, 56; P-R, 0.16 second; QRS, 0.08 second; slurred R in Leads I and II; left axis deviation, suggestive of left ventricular enlargement; and inverted T in CF_4 suggestive of myocardial disease in anterior ventricular wall.

Diagnosis: arteriosclerotic and hypertensive cardiovascular disease; left ventricular enlargement; coronary arteriosclerosis; prodromal stage of coronary artery occlusion.

Treatment: rest in bed (with bathroom privileges); 1/100 grain of nitroglycerin for relief of pain, and triturate of morphine sulfate, ¼ grain, to be taken while awaiting arrival of physician if nitroglycerin failed to relieve pain. Phenaminophyllin (phenobarbital, ¼ grain, and aminophyllin, 1½ grains), one tablet every four hours four times a day, was prescribed.

The patient remained at home, but not constantly in bed on February 9, 10, and 11, and then, contrary to advice, worked (without discomfort) on February 12. He felt well on Sunday, February 13. On Monday, February 14, whilst in a streetcar on his way to work he began to have very severe pain across the front of the chest and in both shoulders and arms. He returned by streetcar and walked about one-eighth of a mile from the streetcar to his home, arriving in a state of shock. The pain persisted and grew in intensity; he perspired profusely and his color was ashen gray during the sixty minutes he spent on this journey. After reaching his home, at 8:00 A.M., he initiated vomiting by putting his finger in his throat; this gave no relief. Vomiting recurred spontaneously and his wife reported

she observed clots of blood in the vomitus. His physician, Dr. Nelligan, came at 10:30 A.M. and found signs of shock. Scarcity of hospital beds delayed his admission to a hospital, until he was brought to the Montreal General Hospital at 5:30 P.M. The pain had persisted all day. He had no dyspnea and he remained clear mentally while in the ambulance. About five minutes after reaching the hospital and while still on the carrier stretcher in the admitting officer's examining room, he suddenly expired. The autopsy was performed by Dr. J. Pritchard, and the following is an abstract of his report.

Both pleural cavities were almost entirely obliterated by fibrous adhesions; there was no evidence of hemorrhage in the gastrointestinal tract; and no evidence of renal arteriolar sclerosis was found. Numerous liver cell nuclei revealed glycogen vacuolization. One small area of hemorrhage and one of softening appeared in microscopic sections of the hypothalamus. Cardiovascular system: maximum transverse diameter of the heart in situ was 13 cm. and of the chest cavity, 28 centimeters. The pericardium was adherent anteriorly to the sternum and the pericardial cavity contained 300 c.c. of blood and clot. On the anterior surface over the region of the interventricular groove at a point 5 cm. from the apex, a perforation 1 cm. in diameter was found; its edges were ragged and the muscle surrounding it, soft and flabby. A probe passing through it could enter either the right or left ventricle.

Fig. 5.—Case 4. Cross-section of left anterior descending branch of the left coronary artery, through the region which grossly appeared to contain the thrombus and is situated in the vicinity of cardiac rupture. Considerable lymphocytic infiltration in adventitia; on one side a large atheromatous plaque lies in the thickened fibrosed intima; the media over this plaque is very thin and atrophic; opposite this plaque the continuity of the arterial wall is broken by what appears to be a "blow-out" with edges turned outward. In and near the thick intima there is marked hematoxylin staining of tissue suggesting iron, the remains of old hemorrhage. In the arteriosclerotic plaque there are foam cells, many free red blood cells and hemosidirin pigment. In the lumen there is a small fibrin clot enmeshing red blood cells, but no platelets.

On opening the heart, a perforation, measuring 0.5 cm. in diameter was found in the interventricular septum, communicating with the tear in the left ventricular wall. The cut surface of the muscle revealed no gross evidence of old or recent infarct; the muscle was uniformly brownish red, and, near the perforation, it was soft. The coronary arteries were everywhere patent, revealing little arteriosclerotic changes with the exception of the anterior descending branch of the left coronary artery; in this vessel, beginning 2.5 cm. from its origin and extending for 1 cm., there was a thick arteriosclerotic patch and a thrombus which together occluded the lumen. Microscopic examination of this region revealed evidence of old and recent hemorrhage into the arteriosclerotic plaque; large foam cells, free red blood cells, and hemosiderin pigment; marked atrophy of the media and a defect in the arterial wall whose edges were turned outward, very strongly suggestive of rupture (a "blow-out") (Fig. 5). A small fibrin clot enmeshing red cells, but revealing no platelets, appeared attached to the intima of the artery. Serial sections revealed marked stenosis of the artery by arteriosclerotic plaques, but the arterial wall was intact, except in the one region described previously. Microscopic examination of the myocardium revealed no evidence of recent or old myocardial in-

farction, but only infiltration of blood causing rupture and separation of muscle fibers in the vicinity of the myocardial tear (Fig. 6).

The evidence of recent and old hemorrhage into the arteriosclerotic plaques of the anterior descending branch of the left coronary artery indicates that the onset of cardiac pain on walking was due to reduction in the size of the arterial lumen in these regions. The terminal attack of pain was most likely due to rupture of the arterial wall and gradual tearing of the myocardium until the ventricular cavities communicated with the pericardial cavity, producing tamponade and sudden death.

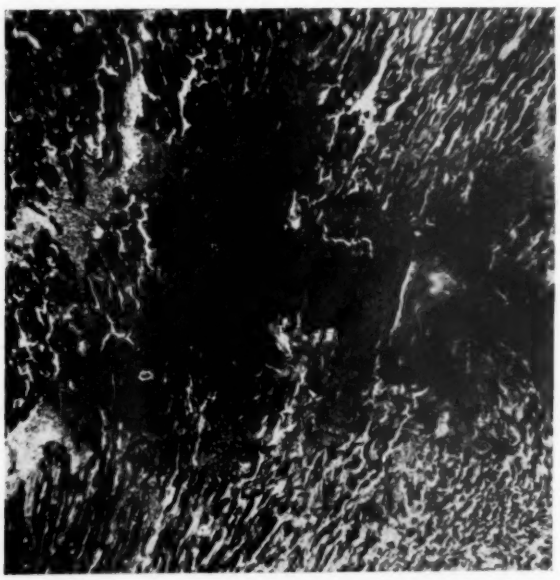

Fig. 6.—Case 4. Section of left ventricle at softened, hemorrhagic, ruptured area. Note well-preserved muscle and hemorrhagic areas disrupting muscle architecture. No muscle necrosis and no cellular inflammatory exudate.

DISCUSSION

Statistical analyses of the incidence of cardiac rupture reported by different authors vary considerably.[2-7] The ideal pattern of facts should include the number of people in the community served by the medical observer or observers; the number of individuals older than 45 or 50 years and, therefore, candidates for coronary artery disease; the number of patients with symptoms or signs of coronary artery disease; the number with episodes of myocardial infarction; and, finally, an autopsy should be done on every case of death in the community in order to determine the number of cases with cardiac rupture. No such statistical analysis is to be found in the literature. Our own experience does not permit presenting such a pattern of facts. Three of the four cases of cardiac rupture belong to a group of about 12,000 patients (private, consultant, and hospital practice), of which about 1,000 had symptoms or signs of coronary artery disease. Four hundred fifty of these presented the clinical picture of myocardial infarction; there were 190 deaths and 49 autopsies. Thus, the clinician at the bedside would be justified in thinking of cardiac rupture in terms of three cases in 450 of myocardial infarction; whereas the pathologist about to perform the autopsy on a case of myocardial infarction would think of the incidence in terms of three in 49. The exact incidence cannot be determined without ideally collected statistics. In the light of present knowledge,

it appears justifiable to look upon myocardial rupture as a rare phenomenon, when thinking about the patient during the course of his illness. Between 70 and 80 per cent of all reported cases of cardiac rupture, were found in people over the age of 60 years. This statistical fact should be of some value in diagnosis and in estimating prognosis.

The conditions under which cardiac rupture occurred were mentioned in only 88 of the 632 cases collected by Krumbhaar and Crowell: eleven during violent conditions (severe overexertion, two; convulsions, three; trauma, three; and cardiac pain, three); 21 during sleep, and the remaining 56 during the mild activities or rest of everyday life. These statistics are inadequate to indicate the relationship of any particular form of exertion to cardiac rupture, but reveal the fact that absolute rest, as during sleep, does not prevent it. In three of our patients it occurred during absolute rest in bed; in the fourth it was initiated while the patient was seated on a streetcar.

The diagnosis of cardiac rupture was suggested in one of our four cases (Case 2), on what seemed to be direct evidence. There is no typical clinical picture or sign. Sudden development of cardiac pain, severe dyspnea, or shock within the first two weeks after the onset of myocardial infarction should suggest cardiac rupture. Paracentesis of the pericardium is a good critical test, which should eliminate or establish the diagnosis, when cardiac rupture is suspected. If there be a special type of murmur produced by the ejection of blood into the pericardium, then this has yet to be clearly described and differentiated from a pericardial friction rub or a valvular systolic murmur. In our case, the peculiar murmur could have been due to pericardial fibrin deposits; it did not resemble that reported by Reznikoff.[9]

Cardiac rupture usually occurs in the anterior ventricular wall, involving the thicker portions of the ventricle and not the apex, where the ventricular wall is thinnest. This suggests that intraventricular pressure does not play the dominant role in determining the difference between a myocardial infarct that does not rupture and one that does. On the other hand, the role of blood pressure was studied by Edmondson and Hoxie,[5] who analyzed data in 72 cases of cardiac rupture in a group of 865 cases of recent infarction, and concluded that patients with hypertension after the establishment of the infarct show a greater tendency to rupture than those who have a low bloood pressure. However, all three of our cases with myocardial infarction had a low or normal blood pressure. This experience leads us to believe that the particular site at which tearing is initiated is of greater importance than intracardiac pressure in determining cardiac rupture. If one assumes that a high blood pressure in the presence of a myocardial infarct is a significant determining factor, then one must explain the absence of rupture in patients who do show marked hypertension for many hours or days after the infarct develops, and in those who ignore their symptoms and continue performing heavy work. The observations made by Lowe[8] on the muscle bundles of the heart suggest that rupture depends upon the point at which tearing is initiated. It is very likely that tears of the myocardium occur in most cases of infarction, but continuation of the tearing process until the entire thickness of the wall is involved must depend upon the plane in which it is initiated.

CONCLUSIONS

Four cases of ventricular rupture have been described. Three were through the left ventricle and occurred within the first six days after coronary artery occlusion and myocardial infarction, while the patients were at rest in bed;

these three cases had normal or low blood pressures; the fourth appears to have followed rupture of the anterior descending branch of the left coronary artery. Cardiac rupture occurs relatively rarely. The determining factor is probably the plane of myocardial muscle in which tearing is initiated. Absolute rest does not prevent cardiac rupture. The clinical diagnosis mainly depends upon pericardial paracentesis, when the condition of cardiac rupture is suspected. The general policy of treatment of coronary disease with myocardial infarction should not be determined by the fear of cardiac rupture, but rather by the probability that it will not occur.

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INTERVENTRICULAR SEPTAL DEFECT (ROGER'S DISEASE) OCCURRING IN A MOTHER AND HER SIX-MONTH FETUS

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THE present communication is the report of identical congenital cardiac lesions occurring in a 20-year-old mother and in her 6-month fetus. In each instance the lesion was a defect in the interventricular wall (Roger's disease) occurring at the base of the heart in the so-called "undefended space." This lesion was diagnosed during life in the mother and proved by autopsy, while the lesion in the infant was also demonstrated at autopsy.

It is generally stated that the etiology of most cases of congenital heart disease is unknown. Heredity has often been mentioned as a possible factor, although few cases have been described as occurring in parent and offspring or in siblings. Vierordt[1] quotes Potocki, who described the case of a man, aged 29 years, who had pulmonary stenosis and an interatrial septal defect and whose mother had congenital heart disease of an undetermined type. Vierordt also

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gives a series, reported by Rezek, of eight cases of heart disease, in two instances congenital, occurring in four generations of a family. Walker[2] describes the case of a father, aged 48 years, and son, aged 18 years, each of whom had the classical signs of coarctation of the aorta.

Abbott,[3] in a study of 850 cases of congenital heart disease, found that a history of congenital heart disease in the ancestry was much less common than was one of cardiac defect or other anomaly in other members of the same generation. In this series there was a history of congenital defect in a sibling in eleven cases. De la Camp[4] described a family in which six children suffered from patent ductus arteriosus, and Gurlee[5] referred to Kushoff's report of another family in which there were similar cardiac defects in six children in the same family. Smith[6] described patent ductus arteriosus in each of identical twins as demonstrated at autopsy and commented on an account by Pezzi and Carugati[7] of adult identical twins, both of whom had dextrocardia. Ellis[8] examined two sisters, aged 9 years, 6 months, and 5 years, 3 months, in whom the diagnosis of patent ductus arteriosus was made on the basis of the clinical signs, while Stern[9] described dextrocardia as occurring in brothers.

Further suggestive evidence that certain cases of congenital heart disease are due to inherent defects in the germ plasm is the not uncommon association of other congenital defects with congenital cardiac abnormalities. For example, in Vierordt's series of 700 cases of congenital heart disease there were 80 cases with associated anomalies, while in Abbott's[10] series of 1,000 cases, 188 had associated anomalies elsewhere in the body.

It is quite possible that the paucity of reports of congenital heart disease occurring in succeeding generations is due to the fact that relatively few individuals suffering from congenital heart disease reach an age at which reproduction normally occurs.

CASE REPORT

The patient, J. K. (B.C.H. No. 1,002,175), a 20-year-old white woman, para 1, entered the hospital on Oct. 22, 1940, complaining that she had fainted without warning.

The patient stated that at the age of 4½ years she was seen at the Boston Children's Hospital because of bilateral congenital inguinal hernias. The hospital record indicates that the patient was slightly cyanotic and dyspneic at that time. On physical examination she was poorly developed and undernourished. The heart was slightly enlarged to the left and to the right. A systolic murmur was heard with the point of maximum intensity at the left border of the sternum just below the level of the third rib. A systolic thrill was palpable in this same area. The liver was slightly enlarged. There was no clubbing of the fingers. There were bilateral inguinal hernias. Because of the cardiac findings it was felt advisable to postpone surgical repair of the hernias. A diagnosis of patent interventricular septum was made, and the parents were advised to restrict the patient's activity.

Eleven years later (1936) the patient was seen at the Boston City Hospital because of discomfort from the hernias. It was felt her cardiac status at this time was such that she could undergo an operation, and the hernias were repaired without cardiac or other postoperative complications.

The patient continued to be cyanotic upon occasion, and the cyanosis was always aggravated by exercise and cold weather. She had an occasional nosebleed but never noticed any edema of the legs or ankles or dyspnea, and she did not find it necessary to restrict her activity.

At the time of admission she said that she was six months pregnant. She had suffered from attacks of intense cyanosis and extreme dyspnea since the onset of gestation. These attacks were more frequent and more severe as her pregnancy progressed. The first episode of syncope occurred on the day of admission, and this so alarmed her that she sought immediate hospitalization.

The past history was of interest in that the patient had frequent attacks of bronchitis as a child. The family history, as far as could be determined, was entirely free from cardiac disorders.

Physical Examination.—The patient was a normally developed, well-nourished, white woman in respiratory distress. Her skin was moderately cyanotic, and this was most marked about the face and extremities. There was moderate clubbing of the fingers. There were a few basal inspiratory râles heard over the posterior lung fields. Auscultation of the heart revealed a gallop rhythm and a loud systolic murmur over the upper third of the precordium, with the point of maximum intensity along the left border of the sternum at the level of the third rib. There was a palpable thrill over this area. The blood pressure was 120/70. An abdominal mass arising in the pelvis and extending to the umbilicus was felt. No fetal heart sounds could be heard.

Hospital Course.—Despite oxygen therapy the patient remained dyspneic throughout the day of admission and complained of feeling very ill and of having severe pain in the right shoulder. Suddenly, during the night, her color changed from a deep cyanotic purple to a pallid blue; the patient failed to respond to emergency stimulants and expired.

Laboratory Findings.—The hemoglobin was 95 per cent (Salhi); the red blood cell count, 5,300,000; and the white blood cell count, 7,500. The differential count and smear were considered normal. The urine was negative.

Autopsy (A40-860).—The body was that of a normally developed, well-nourished, 100-pound woman. There was moderately diffuse purplish discoloration of the face, hands, and lower extremities. There was slight clubbing of the fingers. There was no peripheral edema. The breasts were hypertrophied and were consistent with mid-gestation. There were old healed right and left inguinal operative scars. The abdomen was enlarged by a midline mass which extended to the umbilicus, and when the peritoneal cavity was opened this mass was found to be the uterus, extending 25 cm. above the symphysis. The liver was 8 cm. below the tip of the xiphoid process of the sternum. In each pleural cavity there were 300 c.c. of clear, yellow fluid. The pericardial cavity was essentially negative.

The heart weighed 500 grams. All chambers were dilated. The epicardium was smooth and glistening. The wall of the right ventricle was markedly hypertrophied. A defect measuring 2 cm. in diameter was present in the superior anterior portion of the interventricular septum. In the left ventricle the opening presented beneath the left posterior and anterior cusps of the aortic valve in the fibrous or so-called undefended space (Fig. 1). The upper margin of the defect reached to the base of the aortic cusps. In the right ventricle, the defect presented beneath the medial cusp of the tricuspid valve, the upper margin of the defect extending 0.3 cm. above the free edge of the valve leaflet. The endocardium of the right ventricle over the area opposite the defect was thickened and opaque. The valves were not remarkable. The coronary arteries were thin walled and patent. The ductus arteriosus was represented by a narrow fibrous strand, 0.2 cm. in diameter, and was totally occluded. The foramen ovale in the intraauricular septum had a 0.3 cm. patency anatomically but was considered to be functionally closed. The cardiac measurements were:

Tricuspid valve	13.0 cm.
Pulmonary valve	7.5 cm.
Mitral valve	12.0 cm.
Aortic valve	8.0 cm.
Left ventricle	1.1 to 1.5 cm.
Right ventricle	0.8 to 1.0 cm.

The right lung weighed 540 grams, and the left, 440 grams. Both lungs were similar and were dark red, boggy, and subcrepitant throughout. When cut, the parenchyma was extremely dark red in color and bloody; frothy material was expressed upon pressure. The trachea and main bronchi contained a small amount of mucoid material. The pulmonary arteries and veins were not remarkable.

A 3-cm. Meckel's diverticulum was found 90 cm. from the ileocecal valve. The remainder of the gastrointestinal tract was negative.

The liver weighed 1,720 grams. The organ cut with usual resistance, and the parenchyma was red brown with moderate accentuation of lobular markings.

The kidneys weighed 250 grams, combined. The capsules stripped readily leaving a red-brown surface which was smooth except for several depressed scars on both kidneys, with a deeper red brown, coarsely granular base. On section the kidneys presented a slightly narrowed cortex, 0.4 cm. in width. The cortico-medullary markings were distinct. The pelves and ureters were negative.

The adrenal glands were negative.

The genital organs were consistent with the date of the gestation. There was 1.5-cm. corpus luteum in the right ovary. The other ovary and tubes were not remarkable. The uterus measured 30 by 20 by 20 centimeters. Its wall was 0.8 cm. in thickness. The organ contained a female fetus, 31 cm. from crown to heel. The placenta was 15 cm. in diameter and attached to the posterior wall of the uterus. The placenta and membranes were negative.

Microscopic Examination.—Sections of the maternal heart were not remarkable except that the endocardium over the area in the right ventricle opposite the septal defect showed moderate fibrosis.

Sections of the lung showed a small amount of serum precipitate and some pigment-laden macrophages in the alveoli. There was clublike dilatation of the intra-alveolar capillaries with marked engorgement and widening of the capillary bed. In other focal areas there were sections of alveolar wall that were avascular and fibrous and thickened to approximately twice the usual width.

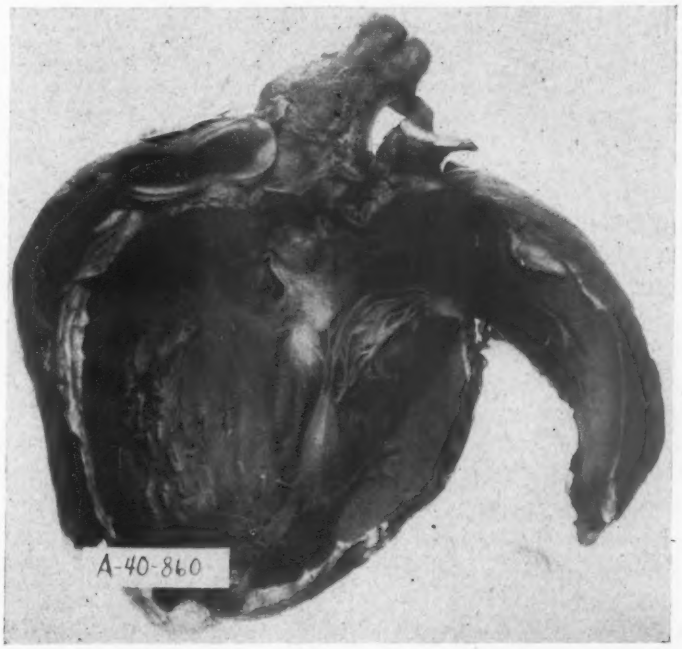

Fig. 1.—Gross photograph of the mother's heart illustrating the interventricular septal defect.

There was extreme hyperplasia of the walls of some arterioles with vascularization of the outer layers of the wall, and fibrin and polymorphonuclear leucocytes present directly beneath the intima. Other arterioles showed less acute reaction with lymphocytes, fibrosis, and marked narrowing of the lumina. The large pulmonary arteries showed no evidence of atherosclerosis.

The liver, aside from a moderate amount of central vein congestion, was not remarkable.

The kidneys were similar in microscopic appearance. The parenchyma was normal throughout, except for the areas subjacent to the scars, described on gross examination. These areas showed vascularized fibrous tissue with infiltration of lymphocytes and atrophic tubules. The glomeruli in these areas were reduced in number and showed some fibrosis. There were no significant vascular changes in the kidney.

The vertebral marrow showed a suggestion of hyperplasia of the red series, but this was not marked, and the other marrow elements were present in approximately the normal proportion.

In the breast the usual proliferation of acinar elements seen in pregnancy was present. It was not otherwise remarkable.

The usual changes of pregnancy were found in the uterus and sections of decidua and membranes were negative.

The remainder of the organs were not remarkable.

The Fetus.—The fetus weighed 640 grams and measured 31 cm. in length from crown to heel. (Nauwerck, in 1921, gave 434 grams in weight and 28 to 34 cm. in length as average for a six-month fetus.) There was very little vernixcaseosa and a moderate amount of lanugo hair. The skin was bright red and wrinkled about the head.

The fetal heart weighed 4.5 grams. There was a 0.4-cm. interventricular septal defect corresponding exactly, in position and relationships, to the defect described previously in the maternal heart. All other structures of the heart were normally developed and consistent with the age of the fetus.

The fetal organ weights were:

	Grams
Right lung	6.5
Left lung	5.0
Heart	4.5
Spleen	1.9
Liver	34.0
Kidneys (combined)	5.0

Microscopic Examination.—The lung of the fetus showed fetal type of alveolar formation with some lumen development. There was eosinophilic debris in a few of these lumina. There was no evidence of any inflammatory process anywhere in the sections or involving any of the blood vessels.

DISCUSSION

Embryologists have demonstrated that the subdivisions of the heart are completed in that period of development extending from the fifth to the eighth week of fetal life, during which time the embryo grows from 10 to 20 mm. in size (vertex to breech). It is at the end of this period that the closure of the foramen interventriculare takes place. The point of union of the aortic with the interventricular septum just below the adjacent ends of the anterior and left posterior aortic cusps remains transparent and free of muscle throughout post-partum life and is known as the pars membranacea septi or undefended space. The foramen ovale is not closed until post-partum. By the eighth week the valvular apparatus has almost completely developed. During the period from the eighth week of fetal life until birth, the portions of the heart that have been delineated undergo further development, but no marked transformation of the constituent parts of the heart takes place. This statement also holds true for the histologic differentiation of these structures, if the valve apparatus is excepted.

It is evident from the above that the heart described in the present fetus represents a true malformation, since the interventricular septum is always completed by the eighth week of fetal life, while the present fetus was at least 24 weeks old, as demonstrated by the clinical history and by fetal weight and measurements.

A further point of interest rests in the confirmation in this case of the frequent observation that, coexistent with one congenital anomaly, others may also be present. For example, in 1,000 cases reviewed by Abbott in 1932, 188 had other congenital anomalies in conjunction with that residing in the heart. In this case, the bilateral congenital herniae and the Meckel's diverticulum were associated with congenital cardiac defect.

Roger's disease is considered to be the second commonest cardiac congenital anomaly. In Abbott's series of 1,000 cases of congenital cardiac anomalies, localized ventricular defects were found in 274 cases or 27.4 per cent. In these 274 cases, all except 17 of the ventricular defects were at the basal portion of the heart. However, only 50 of these cases were unassociated with other cardiac anomalies. In the two cases described here ventricular defect

was the only cardiac anomaly. It is interesting to note that in Abbott's series of 50 cases in which the septal defect was uncomplicated, the mean duration of life was only 14½ years.

The persistent cyanosis was of interest in this case as it was present throughout life. Ventricular defect is considered to belong to the "acyanotic" group of congenital heart disease, as the shunt in the heart is from the arterial to the venous side. The lesions in the small arteries and arterioles of the maternal lung are apparently of recent date and the type of change and etiology are obscure. It is doubtful that these pulmonary vascular lesions played a role in the production of the patient's lifelong cyanosis. It is interesting to note that no vascular lesions were present in the fetal lung.

SUMMARY

1. A case of interventricular septal defect coexistent in a mother and her six-month fetus is described. The diagnosis in each case was confirmed by autopsy.
2. This case suggests a hereditary influence as an etiological factor in the genesis of certain cases of congenital heart disease.

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THE EFFECTS OF AMYL NITRITE ON THE DOWNWARD T WAVE OF THE ELECTROCARDIOGRAM

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INTRODUCTION

THE inhalation of amyl nitrite often causes the downward T_1 of the electrocardiogram, which is often seen in cases of left ventricular enlargement, to become upright.[1-3] However, no satisfactory explanation has been presented for this interesting effect. Inasmuch as we had previously noted that deep inspiration can also cause the downward T_1 of the electrocardiogram to become upright,[4] we thought it might be of value to ascertain the relationship between the electrocardiographic effects of amyl nitrite and those of inspiration. The results of this survey are presented below.

MATERIAL AND METHOD

We studied the effects of amyl nitrite inhalation in a group of twenty-five cases of hypertension, enlargement of the heart, and a downward T_1. In twenty of these cases respiratory changes were also recorded.

Standard leads, and then unipolar extremity leads (taken with the author's method of obtaining augmented unipolar extremity leads and with his indifferent electrode of zero potential[5]) were recorded with the patient either sitting or semirecumbent. As each lead was taken the patient was instructed to take a deep breath, hold it a second or so, and then exhale. The patient was then given a 5-minim ampule of amyl nitrite to inhale, while Lead I was being recorded. As soon as an increase of heart rate was noted, the series of standard and unipolar extremity leads were taken in rotation. This continued for three or four minutes until after the rate had returned to normal.

GENERAL RESULTS

In order to correlate the changes in the standard and unipolar extremity leads, the following is of value [6, 7]: Although each standard lead records the potential difference between the two extremities used, Lead I tends to resemble the left arm lead, and Lead III tends to resemble the left leg lead, especially if Leads II and III are similar.

Occasionally, auricular premature contractions or ventricular premature contractions were produced by the inhalation of amyl nitrite, although sinus tachycardia was the most common arrhythmia observed. Occasionally no changes in heart rate were observed. This was noted among patients whose hearts were very large. The QRS complex usually deviated toward right axis deviation.

T-WAVE CHANGES

In sixteen of our twenty-five cases, the downward T_1 (and the downward T of the left arm lead) became upright after amyl nitrite inhalation. The effect of respiration was also recorded in fourteen of these cases. In all of these, inspiration also caused the downward T wave to become upright (Figs. 1, 2,

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and 3). As a matter of fact, as shown in Figs. 1 and 2, the amyl nitrite caused changes which are practically identical with those due to deep inspiration. However, in these cases, the tachycardia present after amyl nitrite inhalation was not seen during inspiration. In Fig. 3 not only did the T of Lead I and of the left arm lead become upright after amyl nitrite, but there was also a reversal of polarity of T of the right arm lead from (+) to (–). Although inspiratory studies were done only in the left arm lead in this case, we have often observed this effect of inspiration in the right arm lead in other cases with a downward T_1.[4]

In seven cases, amyl nitrite inhalation caused no significant changes in the T wave. The effect of inspiration was noted in five of these cases. Four of these also had no appreciable inspiratory changes in the T wave, and in one case the effects of respiration were somewhat different from those of amyl nitrite (Fig. 4).

In two cases, one of which is illustrated (Fig. 5), the T wave remained downward in Lead I and in the left arm lead, but in the left leg lead and in Lead III, T, which had been upright, tended to become, or became, inverted (Fig. 5). The effects of respiration, recorded only in the unipolar extremity leads in this case, were very similar to the changes due to amyl nitrite. It may be noted that we have frequently observed such changes in the left leg lead and in Lead III on inspiration in cases of left axis deviation, with or without a downward T_1.[4] Attention may also be directed to the marked changes which occurred in the left leg lead in this case, in contradistinction to the minimal changes observed in Leads II and III.

The effects of amyl nitrite on the T wave in all our cases disappeared within three or four minutes, and the T waves became downward again. The inspiratory changes, of course, regressed as soon as the patient exhaled, and reappeared again on inspiration.

DISCUSSION

Most authors have ascribed the electrocardiographic changes after amyl nitrite inhalation to the fact that it increases coronary blood flow.[1-3] Actually, amyl nitrite not only does this, but also causes a fall in blood pressure, tachycardia, and a decrease in the size of the heart.[9] It is, however, not necessary to explain the electrocardiographic deviations by means of these physiologic changes if we assume that the mechanism responsible for the electrocardiographic patterns seen on deep inspiration and after amyl nitrite inhalation is the same. It must be more than coincidence that, in eighteen of the twenty cases in which comparison between inspiratory and amyl nitrite effects were made, the electrocardiographic changes were practically identical.

It is well known that the effects of respiration on the electrocardiogram are due to rotation of the heart; the apex moves downward and the right ventricle tends to be more anterior (and the apex more posterior) on inspiration.[8]

Assuming that there is rotation of the heart after amyl nitrite inhalation, the mechanism of its production is probably a consequence of the decreased size of the heart. The smaller heart would tend to lie more vertically, and thus rotation (as described for inspiration) would take place. Another factor is the fact that hyperventilation was often observed by us after the amyl nitrite inhalation.

That the tachycardia is not of primary importance is shown by the fact that inspiration causes the same changes without the development of tachycardia. Furthermore, the T-wave changes have been shown to be unrelated to

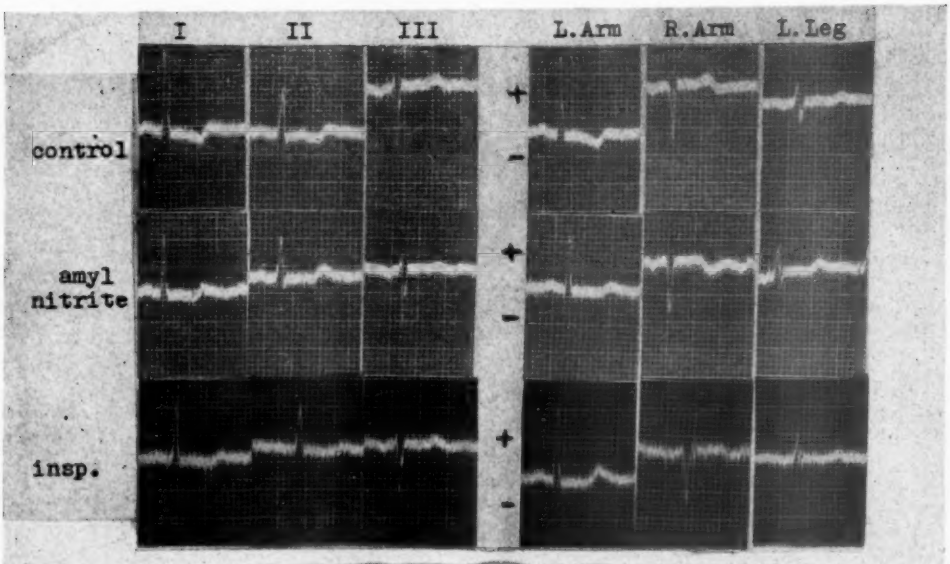

Fig. 1.

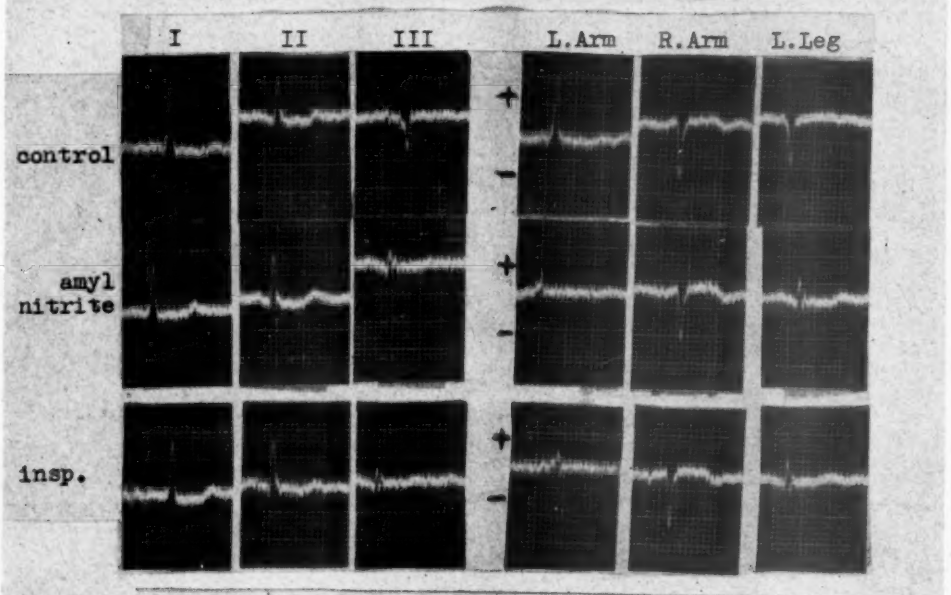

Fig. 2.

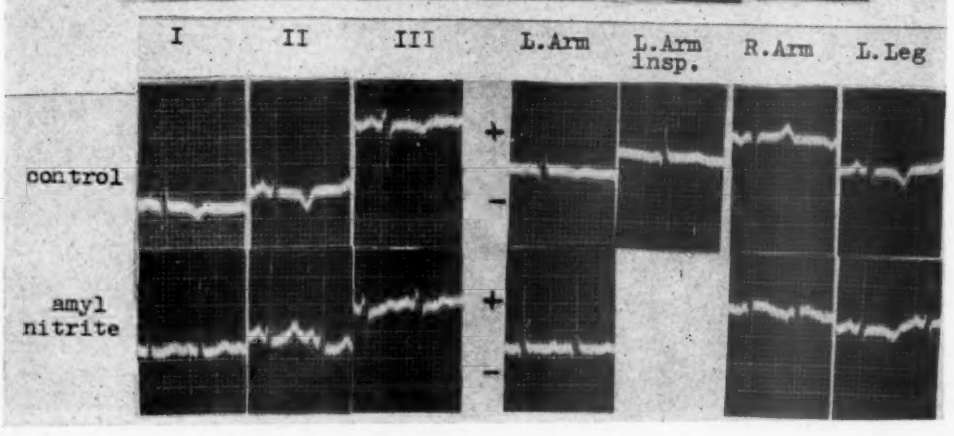

Fig. 3.

(For legends see opposite page.)

Fig. 4.

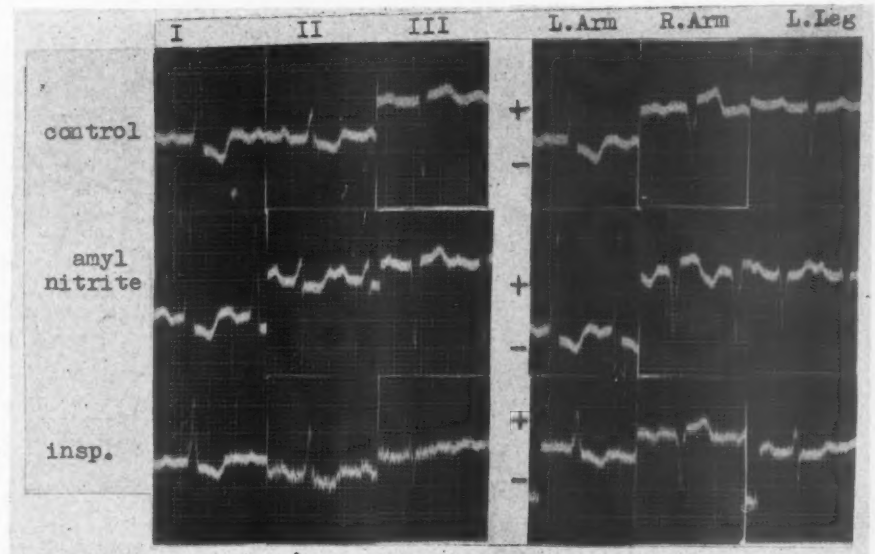

Fig. 5.

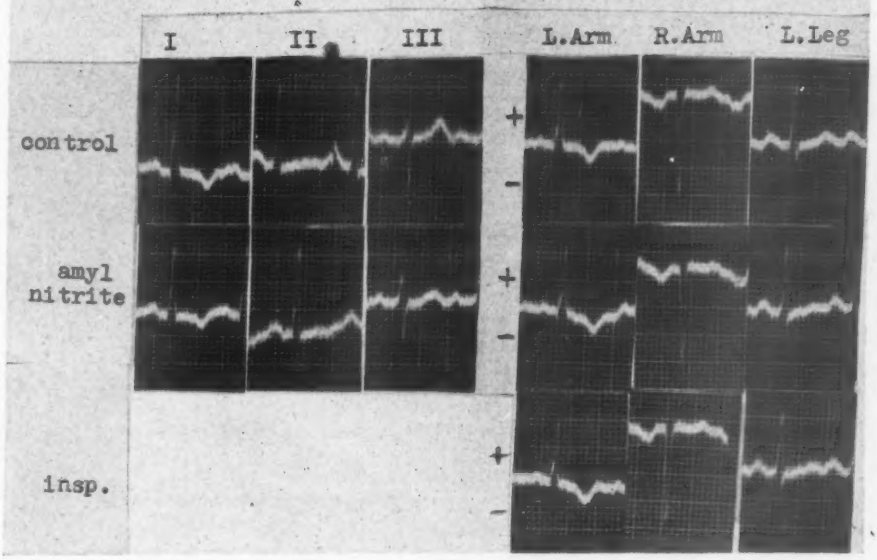

Fig. 4.—F.S., woman, aged 51 years. Hypertensive cardiovascular disease. Upper row, patient semirecumbent, breathing quietly. Middle row, patient semirecumbent, after inhalation of amyl nitrate. Lower row, patient semirecumbent, in deep inspiration.

Fig. 5.—V.B., woman, aged 47 years. Hypertensive cardiovascular disease, cardiac decompensation. Patient had been digitalized. Upper row, patient semirecumbent, breathing quietly. Middle row, patient semirecumbent, after inhalation of amyl nitrite.

Fig. 1.—F.A., man, aged 59 years. Hypertensive cardiovascular disease, cirrhosis of the liver and ascites. Upper row, patient sitting and breathing quietly. Middle row, patient sitting, after inhalation of amyl nitrite. Lower row, patient sitting, in deep inspiration.

Fig. 2.—B.K., woman, aged 75 years. Hypertensive cardiovascular disease. Upper row, patient sitting, breathing quietly. Middle row, patient sitting, after inhalation of amyl nitrite. Lower row, patient sitting, in deep inspiration.

Fig. 3.—F.L., woman, aged 39 years. Hypertensive cardiovascular disease. Upper row, patient lying, breathing quietly. The left arm lead marked "insp." was taken during deep inspiration. Lower row, patient lying, after inhalation of amyl nitrite.

either the heart rate or blood pressure alterations, and may persist even after the heart rate and blood pressure have returned to normal.[1] Although there is no question that amyl nitrite does augment coronary blood flow, the effects of respiration certainly cannot be ascribed to such changes.

A few words might be said about those cases in which amyl nitrite did not cause a reversal of the downward T_1. We noted that this usually occurred when there was marked depression of the RS-T segment, in addition to a downward T_1. In these cases, inspiration was likewise ineffectual in causing a reversal of the downward T wave. This statement, of course, does not answer the fundamental question as to why inspiration should cause a reversal of the downward T wave in one case, and not in another. However, discussion of this is outside the scope of this paper, and will be presented elsewhere.[4]

In the case illustrated in Fig. 4, the electrocardiograms before and after amyl nitrite inhalation are very similar, with the exception of the tachycardia, although inspiration did cause slight changes. It may therefore be assumed that amyl nitrite caused no rotation of the heart in this case.

CONCLUSIONS

When amyl nitrite is inhaled it tends to cause a reversal of the downward T_1 (and the downward T of the left arm lead) which is often observed in cases of hypertension and left ventricular enlargement, and the T wave becomes upright.

These changes usually disappear within three or four minutes.

These changes are similar, if not identical, to those produced by deep inspiration. They can be explained by rotation of the heart, although other factors may take part.

When minor electrocardiographic changes occur, they are often much more marked in the unipolar extremity leads than in the standard leads.

The author wishes to express his appreciation to Dr. Frank N. Wilson, Ann Arbor, Michigan, and Dr. Louis Leiter, who read the first draft of the manuscript, for their valuable suggestions.

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ADDENDUM

We have also observed that in normal subjects with vertical hearts and right axis deviation, both amyl nitrite and inhalation tend to make $T_{2,3}$ downward. Standing also does this. These changes are also due to rotation of the heart. In these cases, forward rotation of the apex around the transverse axis of the heart occurs in addition to the rotation described.

INCIDENCE OF EMBOLIC OR THROMBOTIC PROCESSES DURING THE IMMEDIATE CONVALESCENCE FROM ACUTE MYOCARDIAL INFARCTION

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THE following study was undertaken because of the desire to establish the incidence of embolic or thrombotic processes during the period of convalescence from acute infarction of the myocardium. These conditions include a second and distinct myocardial infarction, pulmonary embolism and infarction of the affected pulmonary tissue, cerebral vascular thrombosis or embolism, thrombophlebitis, and thrombosis or embolism of a peripheral artery. These phenomena, occurring during the convalescent period after coronary occlusion, frequently present serious therapeutic problems, and fairly frequently are responsible for the death of a patient whose recovery seems otherwise assured.

REVIEW OF THE LITERATURE

In any consideration of thrombosis and embolism subsequent to myocardial infarction, attention is directed to mural thrombi, either proved to be, or presumably, located in one or more chambers of the heart. That thrombi are frequently attached to the endocardium subjacent to a region of infarcted myocardium has been noted in many post-mortem studies. Among the earlier records are those of Wolff and White,[1] who stated that a mural thrombus almost always occurs in cases of myocardial infarction; yet in their series of twenty-three cases in which necropsy was performed, thrombi were mentioned in only seven (30 per cent). Levine and Brown[2] reported mural thrombi in thirty-eight (83 per cent) of forty-six cases in which necropsy was performed. Meakins and Eakin[3] reviewed the protocols of sixty-two cases and found mural thrombi in twenty-nine (47 per cent). Bean's[4] study of three hundred hearts in which there were infarcted regions revealed that 47 per cent of them had mural thrombi. Other authors[5-9] have reported finding mural thrombi in from 17 per cent to 66 per cent of cases.

It is agreed that, prior to organization of thrombi, crumbling of the unattached portions loosens particles which may then be swept through the blood channels until they are arrested by the diminishing caliber of the arteries. In the absence of sufficient collateral circulation, infarction results. Since the left ventricle is involved in virtually all instances of myocardial infarction, thrombi occur predominantly in the left ventricle, and whatever emboli arise from such thrombi affect the systemic circulation. Because of the frequency with which portions of the interventricular septum are involved, both chambers are often found to contain mural thrombi. Emboli arising in the right ventricle of course lodge in the lungs.

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In 34 per cent of Bean's cases in which only the left ventricle contained thrombi, emboli were noted in the systemic arteries. He stated that embolism was unusually frequent when a thrombus was attached to the septum. Blumer[10] noted clinically detectable emboli thirty-five times in twenty-seven of 175 cases. The lung was involved sixteen times, and probably in some instances its involvement was the result of emboli from systemic veins. Conner and Holt[11] studied data on 287 cases of coronary thrombosis and noted systemic embolic phenomena in twenty-eight instances.

Emboli arising in the chambers of the left side of the heart may lodge anywhere in the greater arterial tree, but, according to the foregoing studies, they are found most frequently in the spleen, kidneys, and brain. Less often, they affect the mesenteric vessels and the vessels of the extremities. The lodgement of large emboli on the bifurcation of the aorta has been the subject of some recent reports.[12, 13]

A note of caution has been introduced by Blumer, who stated that it cannot be assumed that all arterial occlusions are of embolic origin, but that many must be the result of thrombosis occurring coincident with, or subsequent to, myocardial infarction.

Pulmonary embolism or thrombosis is frequently encountered among patients during the immediate convalescent period. Emboli may arise from mural thrombi of the right auricle or ventricle, or from thrombosis of the systemic veins. In Bean's experience, 75 per cent of the patients with right ventricular thrombi had pulmonary embolism. However, he stated that, in every instance in which massive pulmonary embolism had occurred and had caused death, the emboli had arisen from the veins of the pelvis or lower extremities. Among his three hundred cases, he noted a total of twenty-eight instances of pulmonary embolism, but there is no definite information as to the severity of this complication.

Meakins and Eakin reported pulmonary embolism in twenty-six of their sixty-two cases (42 per cent). This, too, was a study of post-mortem material, and complications are more frequent among patients who eventually die as the result of their illness than among those who recover. Conner and Holt, reporting on 287 cases, including patients who recovered, noted pulmonary embolism in twenty-one instances. Parkinson and Bedford[8] found pulmonary emboli in eight of eighty-three cases in which necropsy was performed and in three of 100 cases ante mortem. Of Blumer's 175 cases, pulmonary emboli were detected clinically in sixteen instances.

Pulmonary embolism is a serious complication of coronary occlusion. Its reported incidence varies from 3 per cent in clinical series to 42 per cent in post-mortem series. It accounts for a relatively high percentage of deaths in the immediate convalescent period. In the series of sixty deaths reported by Woods and one of us (A. R. B.),[14] pulmonary embolism was the cause in six instances. Master, Dack, and Jaffe,[7] in reporting seventy-nine deaths, indicated that nine (11 per cent) were the result of pulmonary embolism. Five per cent of the three hundred patients in Bean's series died of pulmonary embolism.

Much attention has been directed to those cases in which pulmonary embolism occurs postoperatively among surgical patients. Thus, Priestley and Barker[15] found it complicating surgical procedures in 0.52 per cent of the surgical cases. In 0.20 per cent, it was the cause of death. Splenectomy was the operation most frequently followed by pulmonary embolism; the incidence was 3.32 per cent. Embolism caused death in 0.77 per cent of cases, however. In

instances of laparotomy in which surgical procedures were done on the female pelvic organs, embolism occurred in 3.1 per cent of cases. In analyzing deaths occurring in the postoperative period, Priestley and Barker found that pulmonary embolism was the cause of death in 6 per cent of cases. Among 2,381 postoperative deaths in McCartney's[16] series, pulmonary embolism accounted for death in 5.1 per cent of cases.[17] Henderson[18] noted that pulmonary embolism was the cause of death in 6 per cent of his series of surgical deaths during a period of ten years.

On the other hand, Belt[19] reported data on fifty-six cases of pulmonary embolism, forty of which were medical cases and sixteen surgical cases. In 25 per cent of the fifty-six cases the patient had heart disease. Hines and Hunt,[20] in studying 234 cases of death from heart disease, found pulmonary infarcts in 34 per cent. The majority of patients had congestive heart failure. Thus it would seem proper to devote more attention to pulmonary embolism in medical cases, particularly in those in which the heart is diseased.

The literature contains few references to the occurrence of a second myocardial infarction during immediate convalescence from a previous infarction. Blumgart, Schlesinger, and Zoll[21] reported data on two cases in which fresh thrombi were found in the coronary arteries, and in which the patients had suffered recent acute myocardial infarction. Both patients were in a state of shock and one had congestive failure. Most of the reports concerning complications of coronary occlusion do not mention a second attack during the immediate convalescent period.

Thrombophlebitis is frequently mentioned as complicating coronary thrombosis. Harrington and Wright[22] noted it in five of 148 cases, and thought it added gravity to the prognosis. It was present in nine (15 per cent) of Meakins and Eakin's[3] sixty-two cases in which necropsy was performed. Conner and Holt[11] reported venous thrombosis in four of their 287 cases.

Among factors influencing the occurrence of thrombophlebitis are reduction of blood pressure and rest in bed. These conditions reduce venous blood flow. Fall of blood pressure is one of the cardinal signs of myocardial infarction, and the lower level has been shown to be maintained for several weeks. During this period, patients are confined to bed and usually are cautioned to be as quiet as possible. Thus the venous blood is denied the impetus usually imparted by contractions of the skeletal muscles and by frequent changes of position. It would seem that patients confined to bed after coronary occlusion would show a high incidence of venous thrombosis or thrombophlebitis.

Barker and his associates[23-26] correlated the incidence of thrombophlebitis and pulmonary embolism as they occur postoperatively, and found that in 16 per cent of their cases of thrombophlebitis pulmonary embolism occurred, and that in 6 per cent the embolism was fatal. They and others have pointed out the difficulty of detecting clinically the presence of thrombophlebitis, and the true incidence is believed to be higher than is generally recognized.

SELECTION OF CASES

For this study there were chosen one hundred consecutive cases of coronary occlusion encountered at the Mayo Clinic from January, 1940, to May, 1943, inclusive. The criteria for diagnosis included an attack of severe substernal pain, accompanied by sweating, pallor, and fall of blood pressure, and sometimes by collapse. In all instances, positive electrocardiographic evidence was present. In those instances in which death occurred during the period of ob-

servation and necropsy was performed, the clinical diagnosis was substantiated by the morphologic observations. Furthermore, only patients were selected who had entered one of the hospitals in Rochester, Minnesota, within a few days of the acute attack and had remained for a period of at least two weeks, unless death occurred prior to the conclusion of that period. In no case were anticoagulants used. Eighty-two of the patients were residents of Rochester or lived within a 25 mile (40 kilom.) radius of the city, an area for which the Clinic is the natural medical center. The remaining eighteen lived in more distant places, but they adequately fulfilled the other criteria for acceptance. A special effort was made to exclude cases in which there was the slightest suggestion that the patients might have come to the Clinic because of the severity of the original attack or because of the development of complications. In the cases accepted, complications occurred among 36 per cent of the eighty-two local residents, and among 38 per cent of the nonlocal residents. We believe that the cases represent an average group of patients similar to those seen in any city of comparable size located in a predominantly rural sector.

After the cases had been selected, the clinical records were examined carefully for evidences of complications involving the vascular system. Rigid criteria for the actual occurrence of a complication were established. In those instances (eleven) in which death occurred and necropsy was performed, the protocols of the post-mortem examination were reviewed. In addition, the hearts were examined to verify the presence of myocardial infarction. In two cases of death, necropsy was not performed. In those instances (eighty-seven) in which the patients recovered and were dismissed from the hospital, the following requirements for diagnosis of a vascular complication were set:

1. *Subsequent Myocardial Infarction.*—The diagnosis indicated that a second and distinct myocardial infarction occurred while the patient was in bed in the hospital convalescing from the original attack. Such a diagnosis was made only after the occurrence of prolonged and typical pain, accompanied by a fall of blood pressure, characteristic fever, leucocytosis, and increased sedimentation rate, and by definite electrocardiographic evidence of a second infarction.

2. *Pulmonary Embolism.*—A diagnosis of pulmonary embolism was made when patients experienced a sudden, sharp pain in the thorax, with dyspnea and the development of a pleural friction rub, hemoptysis, and slight fever. In those instances in which roentgenograms were taken, there was positive evidence of infarction.

3. *Cerebral Embolism or Thrombosis.*—When sudden hemiplegia developed, a diagnosis of embolism or thrombosis of a cerebral vessel was made.

4. *Arterial Occlusion.*—This condition was recognized when signs of arterial insufficiency of an extremity developed suddenly.

5. *Thrombophlebitis.*—Such a diagnosis was considered when there were signs of local venous obstruction and inflammation. When deep veins were affected, there were pain and tenderness along the course of the veins, together with swelling of the extremity involved. In those instances in which superficial veins were involved, the thrombosed veins could be palpated and there were local pain, redness, and heat.

SEX AND AGE

Seventy-six of the patients were men, and twenty-four were women. The average age of the male patients was 57.9 years, that of the female patients

was 61.9 years, and that of the entire group was 58.8 years. The youngest patient was thirty-nine years of age, and the oldest patient was eighty-three years old. Table I indicates the ages by decades.

The sex and age distribution of the patients in this series corresponds closely to that in other series of patients suffering from coronary occlusion and myocardial infarction.

PERIOD OF OBSERVATION

Fourteen of the patients were in bed in a hospital when the occlusion occurred. In seven cases the occlusion occurred postoperatively, but in the other seven cases no operation had been performed. In the postoperative group, five patients were convalescing from transurethral resection and two from an operation on the stomach. Of the cases in which no operation had been performed, two patients had mild congestive heart failure, one patient was hypertensive, one had carcinoma of the bladder, one had carcinoma of the larynx, one was undergoing treatment for malnutrition, and one had been hospitalized because of symptoms of impending occlusion.

Of the remaining eighty-six, fifty-one entered the hospital within twenty-four hours of the time of occlusion, five entered during the second twenty-four hours, and thirty entered an average of eight days after the acute occlusion.

BLOOD PRESSURE

Forty-two patients were known by Clinic records to have had antecedent hypertension. Patients were considered to be hypertensive when the blood pressure exceeded 150/100, and when examination of the ocular fundi revealed arteriolar changes associated with chronic hypertension according to the criteria of Wagener and Keith.[27]

Similarly, forty-six patients were known by Clinic records to have normal blood pressure. In twelve cases, no definite information concerning the blood pressure prior to myocardial infarction was available.

TABLE I. AGE OF PATIENTS BY DECADES

AGE (YR.)	PATIENTS
30 to 39	2
40 to 49	19
50 to 59	29
60 to 69	33
70 to 79	15
80 to 89	2
Total	100

PREVIOUS CORONARY DISEASE

Forty-three per cent of the patients gave a history of angina pectoris for periods varying from one month to sixteen years. The average duration of angina had been two years and nine months. Of this group, twenty-one patients were hypertensive. They had had angina an average of three years and ten months prior to their infarction. Sixteen of the patients who had had angina had had normal blood pressure, and the duration of angina had been two years and two months before occlusion occurred. Six of the twelve patients whose antecedent blood pressure was unknown had had angina an average of two years prior to their myocardial infarction. Twelve of the entire group of patients had had one myocardial infarction prior to the one observed here. Three of these patients died during their stay in the hospital.

CONCURRENT DISEASES

Ten patients had diabetes mellitus. Two of them had vascular complications and one patient died. One patient had syphilis and had received treatment for tabes dorsalis. This patient died. One patient had carcinoma of the larynx and one had carcinoma of the urinary bladder. The remaining patients had no other significant disease.

LOCATION OF INFARCT

The position of the infarcts was ascertained by using the Q-T patterns according to the method of one of us (A. R. B.[28]). Fifty-two per cent of the infarcts were thus found to be in the anterior apical portion of the left ventricle, and 41 per cent were found to be in the posterior basal portion. In 7 per cent of the cases, the electrocardiogram was thought to indicate acute infarction, but the locations were not definitely established. Six of these patients died, and, at necropsy in each case, acute infarctions were found in the interventricular septum.

VASCULAR COMPLICATIONS

Of the one hundred patients, 37 per cent suffered from complications of a thrombotic or embolic nature. Twenty-eight per cent of the total group had only one complication, whereas 9 per cent had multiple complications (Table II).

Fifteen patients had a second and distinct myocardial infarction. In twelve instances, the second infarction occurred during the fourth to the thirteenth day after the first infarction, whereas, in the remaining three cases, the second infarct occurred on the twentieth, twenty-ninth, and sixty-eighth day, respectively. Of the fifteen patients with multiple infarctions, ten had had normal blood pressure prior to their first infarction. Thus, 22 per cent of the patients who had had normal pressure prior to the first myocardial infarction had subsequent occlusion of a coronary vessel with consequent myocardial infarction. On the other hand, only 5 per cent of the hypertensive patients had subsequent coronary occlusion and myocardial infarction. Among the patients whose antecedent blood pressure was unknown, there occurred second infarctions in three instances (25 per cent). A second infarction caused the death of one of the patients, a 43-year-old man who had normal blood pressure.

Pulmonary embolism and infarction occurred fourteen times in the entire group; it affected seven patients who had hypertension and six patients who previously had had normal blood pressure, and occurred once among the twelve patients whose previous blood pressure was unknown. Pulmonary embolism was the cause of death in one instance. Embolism occurred on the fifth day in one case, but, in the remaining clinical instances of embolism and infarction, the embolism occurred during the sixteenth to the thirty-seventh day.

TABLE II. INCIDENCE OF VASCULAR COMPLICATIONS IN 100 CASES OF ACUTE MYOCARDIAL INFARCTION; TOTAL PATIENTS WITH COMPLICATIONS, THIRTY-SEVEN

COMPLICATIONS (MULTIPLE IN SOME CASES)	INCIDENCE
Second myocardial infarction	15
Pulmonary embolism	14
Cerebral vascular accident	8
Thrombophlebitis	7
Peripheral arterial occlusion	4
Total complications	48

TABLE III. COMPLICATIONS WITH RESPECT TO PATIENT'S PREVIOUS BLOOD PRESSURE

COMPLICATION	NO HYPERTENSION		HYPERTENSION	
	CASES	PER CENT	CASES	PER CENT
Second myocardial infarction	10	22	2	4
Pulmonary embolism	6	13	7	17
Cerebral vascular accidents	1	2	7	17
Thrombophlebitis	3	6	3	7
None	26	57	23	55
Total	46	100	42	100

Cerebral vascular accidents occurred in eight cases. However, among patients who had had antecedent normal blood pressure, they occurred only once (2 per cent), whereas, among patients who had had hypertension, they occurred seven times (17 per cent) and were the cause of death in two instances in the latter group. In both of these cases, necropsy revealed that the vascular occlusion was the result of intravascular thrombosis. This complication occurred during the tenth to the twentieth day in five cases, and on the fourth, seventh, and forty-first days in the remaining three cases.

The left femoral artery of one patient was suddenly occluded on the tenth day after myocardial infarction. This patient subsequently died from pulmonary embolism, and at necropsy no mural thrombus was found. In three other cases infarcts of the spleen or kidneys, or both, were found at necropsy.

Thrombophlebitis was a complicating factor among seven patients, three of whom had had hypertension and three others had had normal blood pressure prior to myocardial infarction. One patient whose blood pressure prior to myocardial infarction was unknown had thrombophlebitis. Five of the patients had subsequent pulmonary emboli and infarction, and an embolus was the cause of death of one of these patients.

Table III indicates the incidence of complications with respect to the level of the patient's blood pressure prior to myocardial infarction.

CONGESTIVE HEART FAILURE

Six patients who had had hypertension had congestive heart failure during at least a part of their hospital stay. Two of these patients had no complications. A third patient had a definite pulmonary embolus on the thirtieth day. The other three patients died, and, at necropsy, one was found to have thrombophlebitis of the systemic veins and multiple pulmonary infarcts. The second patient had mural thrombi in both ventricles and multiple pulmonary infarcts. The third patient had a friable, irregularly shaped embolus in the left pulmonary artery. There was no mural thrombus in this case. The source of the embolus was not ascertained.

Of the patients who had had antecedent normal blood pressure, two exhibited evidence of congestive heart failure. One patient died. At necropsy a right-sided pulmonary infarct and a nonfatal embolus in the left pulmonary artery were found. There was a mural thrombus in the left ventricle. The second patient had no complications. Congestive heart failure was present in one patient whose blood pressure before infarction was unknown. This patient had a pulmonary infarction on the twenty-sixth day.

DIGITALIS

Only twelve of the patients were given digitalis in therapeutic doses. Seven of these had varying degrees of congestive heart failure. In four instances, digitalis was given to patients because decompensation was thought to be im-

TABLE IV. VASCULAR COMPLICATIONS AMONG PATIENTS WHO RECEIVED DIGITALIS

CASE	HYPER-TENSION	CONGESTIVE HEART FAILURE	SUBSEQUENT INFARCTION	PULMONARY EMBOLISM	THROMBO-PHLEBITIS	ARTERIAL OCCLUSION	DEATH
3	Group 2	–	–	Present*	Present	Present	Yes
4	Group 1	Present	–	Present	Present	–	Yes†
5	Group 2	–	–	–	–	Present	Yes†
22	Group 1	–	–	–	–	–	No
23	Group 2	Present	–	Present	–	–	No
31	Group 1	Present	–	Present	–	Present	Yes
37	Group 3	Present	–	–	–	–	No
55	–	–	Present	Present	–	–	No
57	–	Present	–	Present	–	–	Yes†
58	–	Present	–	–	–	–	No
69	–	–	–	–	–	–	No
88	Unknown	Present	–	Present	–	–	No

*Fatal pulmonary embolus.
†Mural thrombus present in heart.

minent but had not yet developed. In one case, 6 c.c. of lanatoside-C (Cedilanid) were given to a patient who had auricular fibrillation. Pulmonary embolism and infarction occurred in five of the seven cases complicated by failure in which the patients received digitalis. Among the five patients who did not have congestive heart failure, three had vascular complications. Five of the twelve patients died. Pulmonary embolism was the cause of the death of one of these. Table IV shows the complications which occurred among the patients who received digitalis.

DEATHS

Thirteen of the 100 patients died during their stay in the hospital. In four cases vascular phenomena were the cause of death: two patients died of cerebral thrombosis, one of pulmonary embolism, and one of a second coronary occlusion. Seven patients died suddenly, and the mechanism of death was not known clinically. Five of these patients were examined post mortem. In four cases there were multiple pulmonary infarcts, and fresh thrombi were found in the pulmonary arteries. In the opinion of the pathologist, these were not the principal cause of death. Two patients died of myocardial failure.

Eleven of the thirteen patients who died were examined post mortem. In seven hearts there were mural thrombi in the left ventricle. Thrombi were

TABLE V. DEATHS

CASE	HYPER-TENSION	CONGESTIVE HEART FAILURE	SUBSEQUENT INFARCTION	PULMONARY EMBOLISM	THROMBO-PHLEBITIS	ARTERIAL OCCLUSION	CAUSE OF DEATH
1	Group 2	–	–	–	–	Cerebral	Congestive heart failure†
3	Group 2	–	–	Present	Present	Femoral	Pulmonary embolism
4	Group 1	Present	–	Present	Present	–	Sudden death*†
5	Group 2	–	–	–	–	Renal	Sudden death*†
8	Group 2	–	–	–	–	Cerebral	Cerebral thrombosis†
10	Group 2	–	–	–	–	Cerebral	Cerebral thrombosis
12	Group 2	Present	–	Present	–	–	Congestive heart failure†
18	Group 2	–	–	Present	–	–	Sudden death*†
31	Group 1	Present	–	Present	–	Renal	Sudden death*
47	–	–	–	–	–	Cerebral	Sudden death*
50	–	–	Present	–	–	–	Coronary occlusion
57	–	Present	–	Present	–	–	Sudden death*†
68	–	–	–	–	–	–	Sudden death*

*In these seven cases, death was sudden and the exact cause was unknown.
†Mural thrombi present.

present in both ventricles in two instances, and, in addition to left ventricular thrombi, auricular thrombi were noted in four instances. Data pertinent to these patients are summarized in Table V.

COMMENT

This series of one hundred cases is too small to allow one to make dogmatic statements concerning the statistical data accumulated. However, such data may be considered suggestive.

Of primary interest is the high (37) percentage of thrombotic or embolic complications. In four instances such complications were the cause of death, and in eight cases these complications were important contributing factors to the death of the patients. Of those patients who had complications and lived, the complicating factor probably had no serious consequences in eight instances. However, in seventeen cases the complications were of definite importance to the patient, for fourteen of them had subsequent myocardial infarction, with further diminution of cardiac reserve, and three other patients became permament invalids because of hemiplegia following cerebral thrombosis or embolism.

Thus, we may say that complications of a vascular nature were of major importance in 78 per cent of the cases in which they occurred. If we consider the entire group of one hundred cases, important complications occurred in twenty-nine cases.

It is also interesting that, in those instances in which a second coronary occlusion and myocardial infarction occurred, ten of the patients had been known to have normal blood pressure prior to the occlusion, whereas only two had been hypertensive. If the second occlusion was of thrombotic origin, it is conceivable that an important precipitating factor could have been the fall of blood pressure after the original occlusion and infarction. Master, Jaffe, Dack, and Silver[29] noted that, in 57 per cent of 538 cases of coronary occlusion, there was a rapid fall of blood pressure, whereas, in 43 per cent, the fall was gradual, and the blood pressure attained the minimal value in one to three weeks. In the majority of their cases, the lowest pressures were reached between the twelfth and the twentieth day. Among persons with normal blood pressure, the systolic pressure fell to less than 100 mm. Hg in 71 per cent of the cases, whereas, among patients who had hypertension, the systolic pressure reached 100 mm. Hg in only 27 per cent of the cases.

From these data, one might postulate that further thromboses would be more likely to occur among persons with normal blood pressure than among hypertensive persons, and, in our cases of a second occlusion, we find such a relationship.

Pulmonary embolism was the cause of death of only one patient. However, it contributed considerably to the death of five other patients. In six cases, there were no apparent serious consequences of embolism. Thrombophlebitis was present in three cases of pulmonary embolism.

Six of the patients who suffered from pulmonary embolism died during their stay in the hospital. Necropsy was performed, and, in four cases, mural thrombi were found in the right auricle or ventricle. The percentage incidence of pulmonary embolism in this series is approximately the same as that reported by other authors in similar series of cases.

In considering cerebral thrombosis or embolism, it is probably significant that this accident occurred in 17 per cent of the patients who had hypertension, but in only 2 per cent of the nonhypertensive patients. In two of the eight

cases in which this complication occurred, the pathologic process was demonstrated by necropsy to be thrombosis. In Bean's cases, cerebral vascular accidents were embolic in six instances and thrombotic in nine instances. Here, too, the postinfarction fall of blood pressure may be a precipitating factor. An additional factor probably is local arterial disease, so commonly found in the cerebral vessels of hypertensive patients.

Factors contributing to thrombophlebitis or venous thrombosis of the extremities have been mentioned previously. For purposes of emphasis, we repeat that they include lowered systemic blood pressure, enforced rest in bed, and lack of movement of the extremities. Clinical investigations on patients who had myocardial insufficiency have indicated a reduced blood flow, and Smith and Allen[30] have reported that the venous circulation is significantly slowed in 82 per cent of cases after major surgical procedures. It may be expected that venous stasis is present in as high or higher percentage of patients who have myocardial infarction.

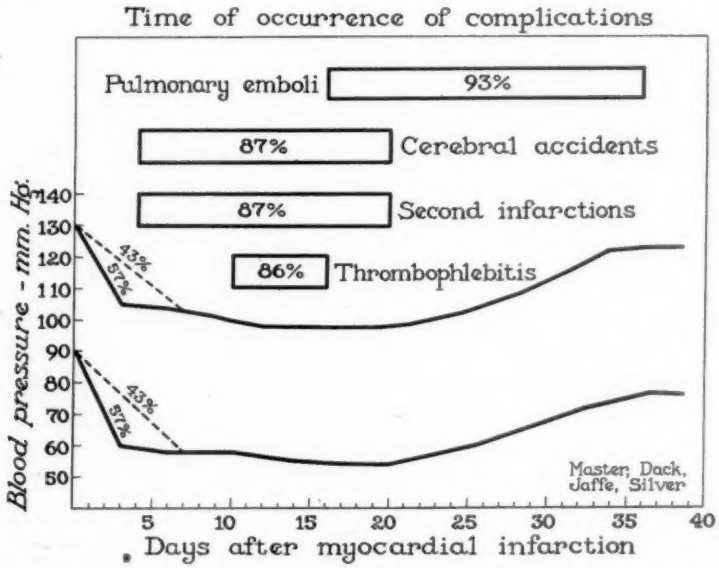

Fig. 1.—Time of occurrence of complications with respect to blood pressure. The parallelograms represent values explained in the paper. The curves are derived from a study by Master, Jaffe, Dack, and Silver.[29]

We believe that it is important to comment on the time of occurrence of the complications which presumably involve thrombosis. Eighty-seven per cent of the instances of second myocardial infarction occurred between the fourth and the twentieth day. Eighty-seven per cent of the instances of cerebral vascular accidents occurred within the same period. Eighty-six per cent of the cases of thrombophlebitis were noted between the tenth and the sixteenth day. It is probably more than coincidence that the great majority of complications occurred during the time that the lowest levels of blood pressure were maintained. This relationship is illustrated in Fig. 1.

Because of the small number of patients who received digitalis, we can only comment with interest on the role of this drug in causing vascular complications. In assaying digitalis, Macht[31] found that, during injection of tincture of digitalis into cats, the coagulation time was progressively shortened from six minutes to one minute and fifteen seconds. He noted a similar effect in assaying ouabain. When he heparinized the cats, he found that the amount of

tincture of digitalis required to cause the heart to stop was increased from 8.5 c.c. per kilogram to 10.2 c.c. per kilogram. This effect he thought was due to prolongation of the coagulation time. Macht concluded that, under certain pathologic conditions, digitalis promotes intravascular clotting and predisposes to thrombo-embolic accidents.

De Takats, Trump, and Gilbert[32] presented data on four cases which they interpreted as illustrating the effect of digitalis on the clotting mechanism. Furthermore, they reported a diminished effect of heparin on both human beings and dogs in the presence of digitalization. In another article, de Takats[33] stated that, after cardiovascular accidents, patients show decreased tolerance to heparin.

Of our group of twelve patients who received digitalis, seven had pulmonary embolism and infarction, and another had multiple infarcts in the kidneys. Detectable thrombophlebitis was present in two cases. It must be remembered that seven of the patients had congestive heart failure, a condition which in itself fosters thrombosis.

Further study is necessary to define clearly the role of digitalis in thrombo-embolic phenomena among human beings.

SUMMARY

One hundred consecutive cases of acute coronary occlusion and myocardial infarction were studied, and the incidence of subsequent intravascular thrombosis or embolism during the immediate convalescent period has been tabulated.

Complications of a thrombotic or embolic nature occurred in thirty-seven cases. In four cases the complication caused the death of the patients, in eight cases the complications were contributing factors in the death of the patients, and in seventeen other cases the complication was of considerable importance in the future health of the persons concerned.

A second myocardial infarction occurred in fifteen cases, pulmonary embolism occurred in fourteen cases, cerebral thrombosis or embolism complicated eight cases, arterial occlusions were noted in four instances, and thrombophlebitis complicated seven cases.

Forty-six of the patients were known to have had normal blood pressure prior to the coronary occlusion and myocardial infarction. Ten (22 per cent) had subsequent myocardial infarctions during the immediate convalescent period. Forty-two of the total group of one hundred patients had had hypertension prior to coronary occlusion, and two (5 per cent) had subsequent myocardial infarctions during the immediate convalescent period. In twelve cases, the blood pressure prior to coronary occlusion was not definitely known. Three of these patients had a second myocardial infarction during their residence in the hospital.

Eighty-seven per cent of the cases of second myocardial infarction and 87 per cent of the instances of cerebral vascular accidents occurred between the fourth and the twentieth day, and 86 per cent of the cases of thrombophlebitis occurred between the tenth and the sixteenth day, periods when the blood pressure of patients who have acute myocardial infarctions has been demonstrated to be at the lowest levels.

Thirteen of the patients died. Two of them died as a result of cerebral thrombosis, one from pulmonary embolism, and one from a second myocardial infarction. Two other patients died of congestive heart failure. In seven instances death was sudden, but the exact cause was not ascertained.

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A CASE OF INFECTION WITH BRUCELLA SUIS, CAUSING ENDOCARDITIS AND NEPHRITIS; DEATH FROM RUPTURE OF MYCOTIC ANEURYSM

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DESPITE the increasing frequency with which brucellosis is being recognized clinically, reports of anatomic studies made at autopsy are rare. In 1937, von Albertini and Lieberherr[1] collected from the literature, and supplemented from their own experience, reports of thirty-nine cases in which pathologic examination had been performed. Of these, fourteen lacked histologic studies and two were examined only by biopsy. The authors included eight cases of their own. It is obvious from their bibliography, however, that they did not review the English literature.

Forbus[2] states, "There are three fairly well-defined types of fatal brucellosis, namely (1) the septicemic or relatively acute form, (2) the focal or localized form of infection, again relatively acute, and (3) the chronic lymphogranulomatous type with prolonged course." In the second type must be included the rarely reported cases of *Brucella* endocarditis.

In 1897, Hughes[3] reported three cases in which endocarditis was found as a complication of infection with what would now be termed *Brucella melitensis.* Scott and Saphir[4] studied a patient with *Br. abortus* bacteriemia who was found at autopsy to have friable vegetations on scarred mitral and aortic valves. De La Chappelle[5] reported the case of a patient whose blood culture was positive for *Br. melitensis A.* The aortic valve was found at autopsy to have fresh vegetations superimposed on old scarring. Casanova and d'Ignazio[6] performed an autopsy on a patient and secured a pure culture of *Br. melitensis* from vegetations on the aortic valve. Ulcerative endocarditis was observed at autopsy by Gounelle and Warter[7] in a patient whose blood culture contained *Br. melitensis.* Rennie and Young[8] studied a patient whose blood contained *Br. abortus.* At autopsy, fresh vegetations were found on a scarred and stenotic mitral valve. In 1938, Levy and Singerman[9] reported the case of a patient whose blood culture yielded *Br. melitensis.* At autopsy, friable vegetations were found on a scarred mitral valve. Smith and Curtis[10] published studies on a patient whose blood cultures were positive for *Br. abortus.* At necropsy, there were ulcerative, thrombotic vegetations on the aortic valve. Patchy areas of calcification were found in the leaflets of the aortic cusps. The interauricular septum was the site of an ulcerated, aneurysmal dilatation. Spink and Nelson[11] studied a patient with brucellosis complicated by endocarditis. At autopsy, vegetations were found on a previously normal aortic valve. *Br. abortus* was obtained in pure culture from these vegetations. Wechsler and Gustafson[12] reported the occurrence of *Brucella* endocarditis on a bicuspid aortic valve. Spink, Titrud, and Kabler[13] obtained a pure culture of *Br. abortus* from vegetations on the mitral valve of a patient who died of brucellosis. Scarring of the mitral and aortic valves and the presence of Aschoff bodies proved the prior

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existence of rheumatic endocarditis. Call, Baggenstoss, and Merritt[14] have recently added reports of two cases in which infection with *Br. abortus* was proved by blood culture. In one, fresh vegetations were found on the aortic valve, and, in the other, on the mitral valve. In both cases there was evidence of pre-existing rheumatic endocarditis.

Involvement of the endothelium other than that of the heart by *Brucella* is apparently even more rare. Mycotic aneurysms of clinical importance have seldom been reported in brucellosis. Rupture of a mycotic aneurysm of the basilar artery was found by Hansmann and Schenken[15] at autopsy on a patient whose cultures of blood and spinal fluid contained *Br. suis*. Knighton[16] reported the case of a man with fever whose blood contained agglutinins against *Br. abortus* and *Br. melitensis* in a dilution of 1:100. A clinical diagnosis of *Brucella* endocarditis was made. A mycotic aneurysm, 6 by 8 cm., involving the right axillary and subclavian arteries, developed. Recovery of the patient was attributed to ligation of the aneurysm.

In their extensive studies on *Brucella* infections in Iowa, Hardy, Jordan, Borts, and Hardy[17] concluded that, in general, *Br. suis* is more virulent for man than *Br. abortus*. From animal inoculation and clinical experience, it has been thought that the porcine strain was also more virulent than the caprine species, *Br. melitensis*. It is therefore remarkable that endocarditis has not hitherto been reported as a complication of infection with *Br. suis*. That the organism attacks endothelium is proved by the case of mycotic aneurysm reported by Hansmann and Schenken.[15] Spink and Nelson[11] considered that in many of the cases reported as *Brucella* endocarditis the diagnosis was not proved. They demanded that such a diagnosis be substantiated by bacteriologic and anatomic evidence obtained at autopsy.

We will report studies on a patient with endocarditis and diffuse nephritis who died from rupture of a mycotic aneurysm. The significant lesions were proved to be due solely to *Br. suis*. The evidence presented meets the rigid criteria set up by Spink and Nelson. As far as we can ascertain, this is the first report of endocarditis proved to be caused by the porcine strain of *Brucella*.

CLINICAL OBSERVATIONS

M. K., a farmer, 45 years old, was admitted to the University Hospital Dec. 10, 1943, in semistupor. His wife said that, during September of that year, malaise and intermittent fever had gradually developed. He had performed his work on the farm, interrupting it with intervals of a few days in bed. After October 6, he had been in bed continuously. His wife had kept a daily record of his temperature; this is included in Fig. 1. During November, his attending physician had administered sulfanilamide for one week with no diminution of fever, or alleviation of symptoms. About December 1, his condition became noticeably worse. He had been alternately delirious and somnolent. An eruption had appeared on the skin, and the ankles had become swollen.

Upon admission to the hospital, examination revealed a well-developed and well-nourished man, 5 feet 4 inches (162.5 cm.) in height, weighing 149 pounds (67.7 kg.). He was stuporous and disoriented. There was some evidence of dehydration. Purpuric areas were present, particularly in the skin over the legs and feet, although there were a few on the upper part of the body. In addition, there was a faun-colored maculopapular eruption which was confluent over the thorax and abdomen. Edema over the ankles pitted to a depth of 5 millimeters. The accessible lymph nodes were not enlarged. There was no pallor, cyanosis, or dyspnea. The eyes appeared normal. The extraocular movements were normally performed. The pupils reacted to light and in accommodation. The ocular fundi contained no hemorrhages, edema, or areas of degeneration. The nose, ears, teeth, and tongue were negative. The neck was not remarkable. The heart was normal with respect to size, rate, and rhythm. The quality of the heart sounds was not altered. A soft, blowing, systolic murmur was heard over the entire precordium. The contour of the peripheral arterial pulse was normal.

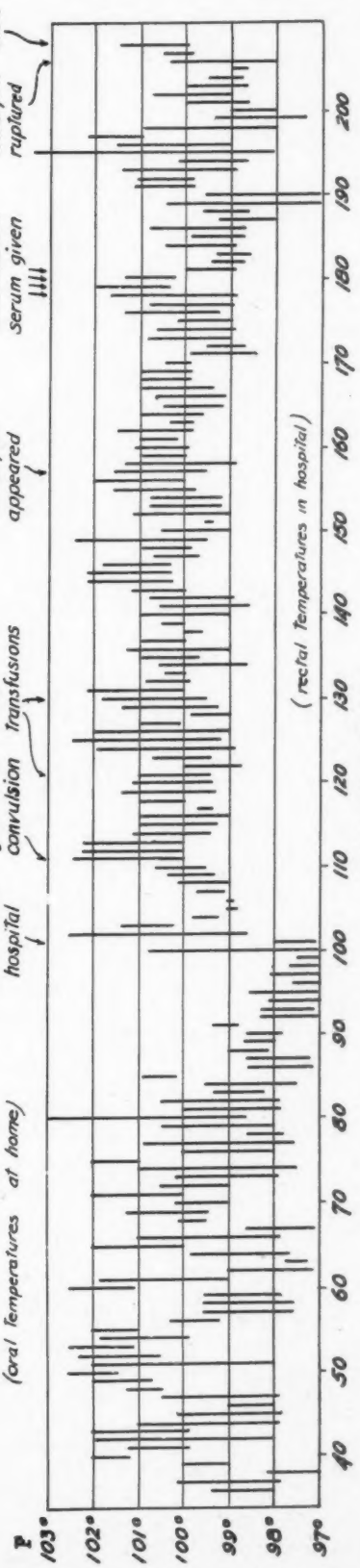

Fig. 1.—Record of daily temperature.

The blood pressure measured 150/82. The lungs were normal. There was some gaseous distention of the abdomen. The liver and spleen could not be palpated. There was no evidence of free fluid in the peritoneal cavity. The genitals and rectum were negative. The prostate was normal in size and consistency. The tendon reflexes were normal. There were no pareses.

The first specimen of urine to be examined was acid in reaction, with a specific gravity of 1.010. It contained no albumin or glucose, but the sediment included many erythrocytes and granular casts. The hemoglobin of the blood measured 10.5 Gm. per 100 c.c. (Haden-Hausser). The erythrocyte count was 2,950,000 per cubic millimeter. The leucocytes numbered 4,700 per cubic millimeter. The differential counts were normal.

A tentative clinical diagnosis of uremia was made. It was thought that the probable cause was focal embolic nephritis due to subacute bacterial endocarditis. The blood urea nitrogen was found to be 74.9 mg. per 100 c.c., and the blood creatinine was 5.5 milligrams. A blood culture, taken to demonstrate the presence of *Streptococcus viridans,* yielded, instead, *Brucella,* uncontaminated by other organisms. An intradermal test with brucellergin gave a negative reaction, as was observed in the cases reported by Spink and Nelson.[11] The blood serum agglutinated *Brucella* in a dilution of 1:640.

There had been no previous history of rheumatic fever or heart disease. The patient had lived on a farm in Iowa, but knew of no evidence of brucellosis in his live stock. While the patient was in the hospital, his cattle were tested for evidence of Bang's disease, but none was found. The hogs were not examined, an oversight of frequent occurrence.

For descriptive purposes, the date of onset of the disease has been arbitrarily assumed to be Sept. 1, 1943. By this reckoning, the patient was admitted to the hospital on the one hundred and first day of the disease. The fluctuations in body temperature, the chemical studies of the blood, and the bacteriologic observations are recorded in the accompanying charts and tables.

Because of the azotemia and hematuria, the patient was encouraged to drink copious amounts of fluids. Within a few days, the daily urinary excretion varied from 1,000 to 3,000 cubic centimeters. By the one hundred and eighth day of the disease, the stupor was diminishing, and he appeared somewhat improved. The blood urea nitrogen and creatinine gradually diminished (Table I). Many examinations of the urine during the course of observation showed that the albumin gradually diminished in amount from 2 plus to a trace. Erythro-

TABLE I

*Blood Chemical Studies During Life**

DAY OF DISEASE	UREA NITROGEN (MG./100 C.C.)	CREATININE (MG./100 C.C.)	MISCELLANEOUS
102	74.9	5.5	Sulfonamide—trace
107	63.7	4.5	van den Bergh: 1.2 indirect
111	46.9	3.4	
113	39.2	4.1	
118	46.9	3.1	
125	32.9	2.4	
132	33.6	2.2	Serum albumin, 2.55 Gm.; globulin, 3.68 Gm.
140	34.3	2.4	
147	24.5	1.8	Urea clearance, 127 per cent
149	22.4	1.7	
157	23.1	1.9	
171	15.4	1.0	
188	14.0	1.0	

Bacteriologic Studies During Life†

DAY OF DISEASE	NATURE OF STUDY	RESULTS
105	Blood culture	*Br. suis*
107	Blood culture	*Br. suis*
110	Skin test with brucellergin	Negative
111	Agglutinins in serum	Positive for *Brucella* in dilution 1:640
114	Urine culture	*Brucella* and *Escherichia coli*
134	Blood culture	*Br. suis*
135	Agglutinins in serum	Positive for *Brucella* in dilution 1:320
178	Blood culture	*Br. suis*
181	Blood culture	*Br. suis*

*Determinations performed by the Department of Pathologic Chemistry.
†Bacteriologic diagnoses by the Department of Bacteriology.

cytes continued to be present in the sediment, but the number diminished with lessening of the azotemia. Some granular and hyaline casts were always present. The values of hemoglobin in the blood fluctuated between 8.5 and 12 Gm. per 100 cubic centimeters. Erythrocyte counts were recorded from 2,950,000 to 4,930,000 per cubic millimeter. The leucocytes varied between 2,800 and 6,050 per cubic millimeter. Serial electrocardiograms were normal except for left axis deviation and increasing negativity of T_3.

The faun-colored eruption disappeared within two days after admission. The edema of the ankles and the purpura subsided soon afterward, never to reappear. On the one hundred and eleventh day, the patient had a generalized convulsion lasting only a few minutes, but accompanied by extreme cyanosis. The blood pressure during the convulsion measured 185/130, but normal levels were afterward resumed. There were no residual neurological signs. It was thought possible that the patient had suffered cerebral embolism. On the one hundred and twenty-second day, a pain developed in the right knee and ankle, and migrated to the right hip. Roentgenograms of the pelvis showed evidence of spondylolisthesis and a separate neural arch; the body of the fifth lumbar vertebra had slipped slightly forward on the sacrum. This lesion was not attributed to brucellosis.

Slight, transient, painful swellings of the left ankle, left knee, right hand, and right knee appeared for periods of a day or so. Blood transfusions were given on the one hundred and twenty-first and one hundred and twenty-eighth days, but they were accompanied by such severe urticaria that repetition of the procedure was not attempted. Another troublesome symptom was an unproductive cough, unaccompanied by physical or roentgenologic evidence of disease in the chest. Some relief was obtained by steam inhalations.

On the one hundred and fifty-seventh day, the patient called attention to a painless mass in the left inguinal region. This proved to be an ovoid, pulsating tumor, 4.5 cm. in diameter, in the region of the left femoral artery, just inferior to the inguinal ligament. All pulsation had disappeared in the left popliteal, dorsalis pedis, and posterior tibial arteries. A clinical diagnosis of mycotic aneurysm of the left femoral artery was made. The size of the mass increased daily, with extension downward along the artery. The left foot and leg, however, remained warm and normal in color. A surgical consultant deemed ligation of the aneurysm inadvisable.

Therapy with sulfonamides was considered to be contraindicated by the renal lesions, and penicillin could not be obtained for the treatment of brucellosis. Convalescent serum was therefore prepared. Through the kindness of Dr. George H. Finch, of Des Moines, Iowa, a group of his patients agreed to serve as blood donors. All of them had recovered from severe infections with *Br. suis*, and bacteriemia had been present in every case, as shown by positive blood culture. Pooled serum was prepared by Dr. Carl F. Jordan, of the Iowa State Health Department, from the blood of ten of these patients. One hundred cubic centimeters of the pooled convalescent serum were given to our patient intravenously on the one hundred and seventy-eighth, one hundred and seventy-ninth, one hundred and eightieth, and one hundred and eighty-first days of the disease. There were no associated reactions. No definite change was noted in the condition of the patient; his temperature did not remain normal and the blood was not freed from organisms.

By the one hundred and eighty-fourth day, the condition of the patient was definitely worse. The aneurysm had attained a diameter of 10 centimeters. The walls appeared firmer. The patient was somnolent most of the time, and paresis of the facial muscles was noted on the right side. The left leg was weak and there was ankle clonus bilaterally. Saline and dextrose solutions were administered parenterally daily, together with thiamine chloride and nicotinamide. Twelve days later he had brightened considerably. The facial paresis had disappeared and his appetite had improved.

On the morning of the two hundred and sixth day, the patient experienced severe pain in the left groin which radiated down the leg. This increased over a period of several hours. Bright blood appeared in the urine. The scrotum became distended with fluid. The general condition, however, appeared good, and the blood pressure was maintained. During the next two days, the scrotum became discolored from extravasated blood. On the afternoon of the two hundred and eighth day, he complained of severe pain in the lower part of the abdomen, and died within an hour.

POST-MORTEM EXAMINATION

Autopsy was performed three and one-half hours after death.

General Inspection.—The body was that of a well-developed, well-nourished man, about 45 years old, showing a moderate degree of lividity posteriorly. Rigor mortis was present. The skin and mucous membranes were slightly icteric. A small amount of dependent edema

was present over the hands and ankles. There was a large diffuse swelling which involved the lower portion of the left lower quadrant of the abdomen and the left inguinal region. The skin in this area was not discolored, but the area of swelling was fluctuant. The scrotum was markedly edematous, and distended to five times the normal size. The skin on the scrotum had a bluish discoloration.

Peritoneal Cavity.—In the long axis of the left femoral artery there was a fusiform sac, 9 by 5 cm., lying both above and below the inguinal ligament. Externally, the sac was covered with adipose and areolar tissue which was heavily infiltrated with blood. Opening the sac revealed that it was lined with a thin, friable, gray membrane lying upon at least two other similar layers which were easily separated. No recognizable media or intima was visible.

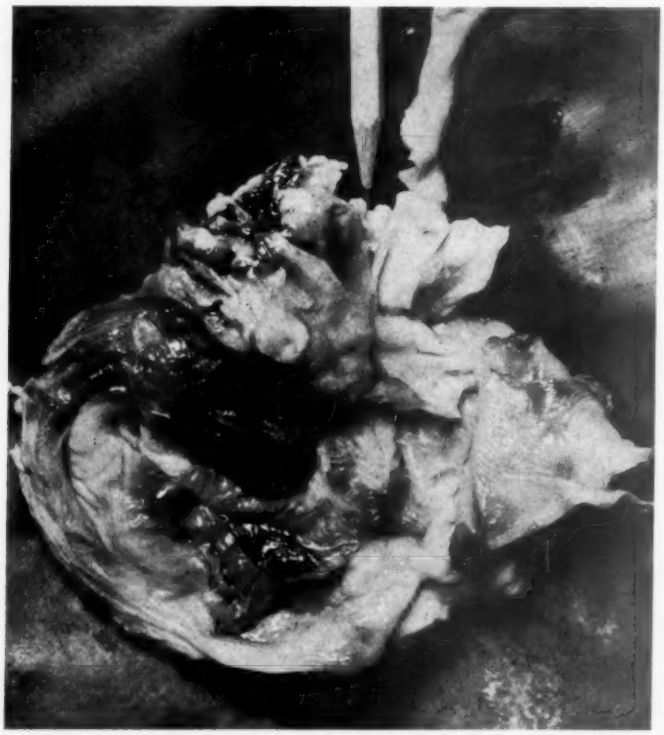

Fig. 2.—Mycotic aneurysm of left femoral artery. Autopsy specimen in which the aneurysmal sac has been opened, showing walls composed of layers of fibrin. The pencil lies parallel to the intact femoral artery superior to the sac.

The femoral artery entered the superior pole of the sac, whereupon its structure was abruptly lost, to be resumed inferiorly (Fig. 2). On the superior surface of the sac was a hole, less than 1 cm. in diameter, through which blood had apparently extravasated into the retroperitoneal tissues along the left lateral portion of the abdominal wall to the left leaf of the diaphragm, spreading into the fan of the mesentery. In these regions the blood was present in clotted masses; the quantity was greatest near the left femoral artery and the left common iliac artery. Extravasation of blood had also occurred beneath the peritoneal covering of the sigmoid and descending colon. The scrotal sac contained a large amount of clotted blood which had infiltrated the fixed tissues. The peritoneal cavity contained about 100 c.c. of serosanguinous fluid, but no clots of blood were present. Microscopic examination of the wall of the aneurysm showed that it was composed of thick layers of fibrin. In some areas, portions of the arterial wall remained, but, for the most part, layers of fibrin were either superimposed on thin, partially hyalinized muscularis, or the fibrin lay directly on adjacent scar tissue. Masses of calcium were present in the muscular wall of the artery. Throughout the hyalinized layers of muscle and fibrin were nests of lymphocytes, monocytes, plasma cells, and large mononuclear cells. Small areas of fibroblastic proliferation were seen.

Pleural Cavity.—Both pleural cavities contained about 100 c.c. of clear, straw-colored fluid. The visceral and parietal layers were smooth and glistening, and no adhesions were present.

Mediastinum.—The organs showed normal relationships and no abnormalities were noted.

Pericardial Cavity.—The sac contained about 100 c.c. of straw-colored fluid. Everywhere the pericardium was smooth and intact.

Heart.—Weight, 350 grams. The size and contour were normal. The epicardium was smooth and intact; the epicardial fat was abundant. The cardiac chambers were normal in size and contained both fluid and clotted blood. The foramen ovale was closed. The endocardium of the left ventricle, beneath the aortic cusps, was slightly thickened and opaque. The measurements of the valves were: aortic, 6.5 cm.; mitral, 12 cm.; tricuspid, 13 cm.; and pulmonic, 6 centimeters. There were moderate, diffuse fibrosis and rolling of the free margins of the mitral leaflets, together with moderate scarring of the chordae tendineae. There was no suggestion of stenosis of the valve, however, and the degree of scarring was not more than is often seen with simple valvular sclerosis. These observations were not interpreted as evidence of rheumatic endocarditis. The anterior leaflet of the mitral valve contained a perforation measuring 7 mm. in diameter (Fig. 3). At the superior margin of the perforation was a friable, grayish-yellow vegetation, 1 cm. in diameter. Smaller, but similar, structures were implanted at the periphery of the perforation. Along the remainder of the line of closure there were small, pebbled masses, more firm and yellow than the large vegtations.

Fig. 3.—Perforation of the mitral valve. The photograph was taken forty-eight hours after the autopsy was performed. The friable vegetations had been removed previously for bacteriologic examination, and the valve leaflets had partially dried, so that they present the appearance of scarring in the photograph.

The vegetations were removed for bacteriologic study. The wall of the left ventricle measured 1.5 cm. in thickness, and that of the right ventricle, 0.5 centimeters. The myocardium was firm and beefy red. No abnormalities were noted on the cut surface. The coronary arteries were patent, but the walls contained occasional atheromatous plaques. With the microscope, moderate fragmentation of muscle bundles could be seen in some areas, but the cells were normal in size. Throughout the myocardium, especially in the interstitial tissue, there were small oval clusters of large, pale mononuclear cells, lymphocytes, plasma cells, and occasional polymorphonuclear leucocytes. These areas were more numerous near the endocardial surface. A few, small, round cells were scattered throughout the muscle fibers. There were no areas of necrosis and no Aschoff bodies. The blood vessels were normal, and the cell clusters bore no relationship to them. A section through a coronary artery showed the usual histologic changes of atherosclerosis.

Lungs.—The left lung weighed 380 grams, and the right, 400 grams. They were similar in appearance. The tissue was fluffy and contained air. A few emphysematous blebs were present along the superior margins. The bronchial mucosa was smooth and intact. There

was present over the hands and ankles. There was a large diffuse swelling which involved the lower portion of the left lower quadrant of the abdomen and the left inguinal region. The skin in this area was not discolored, but the area of swelling was fluctuant. The scrotum was markedly edematous, and distended to five times the normal size. The skin on the scrotum had a bluish discoloration.

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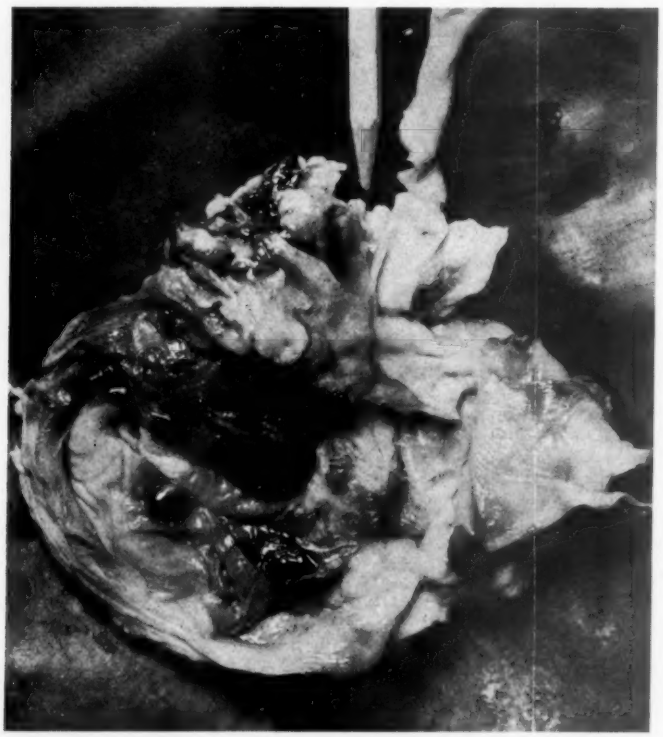

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Lungs.—The left lung weighed 380 grams, and the right, 400 grams. They were similar in appearance. The tissue was fluffy and contained air. A few emphysematous blebs were present along the superior margins. The bronchial mucosa was smooth and intact. There

was no congestion. The tracheobronchial nodes were normal. The cut surfaces of the lungs were dry and grayish pink. Histologic examination revealed that the pleura was normal. Many of the pulmonary acini were distended, and the walls thinned and ruptured. Patchy areas of fibrosis of the alveolar walls and interstitial tissue were numerous. These areas were infiltrated diffusely with lymphocytes, plasma cells, and large mononuclears. The bronchial epithelium in some areas was hyperplastic, and the peribronchial tissue contained zones of mild, chronic cellulitis. The blood vessels were normal.

Spleen.—Weight, 950 grams. The capsule was rather tense, but smooth and intact. The organ was softer than normal. On cut section, the Malpighian bodies appeared to be enlarged. The parenchyma was extremely pultaceous, and was reddish brown. Trabeculation was not visible. Near the lower pole there was a yellow area of necrosis, 1 by 2 cm., surrounded by a zone of hyperemia. A similar area was noted near the upper pole, but the latter was more firm and scarred. Microscopically, the splenic follicles were seen to be hyperplastic, and they contained small, hyalinized areas near their centers. There was diffuse hyperplasia of the reticuloendothelial elements. Throughout the pulp there were clusters of loosely arranged plasma cells, lymphocytes, and large mononuclears in no definite pattern. These masses were poorly circumscribed, but blended with the surrounding pulp. There were areas of congestion and the sinusoids were conspicuous. A large mass of scar tissue in one region contained old blood pigment and scattered round cells. In another section there was a large area of infarction, surrounded by a wide zone of extravasated blood. Fibroblastic proliferation was extensive at the periphery of the infarct.

Pancreas.—The gland was normal in size and consistency. Small, chalky plaques were visible on the cut surfaces. Microscopically, besides a moderate degree of autolysis, there were large areas of fat necrosis, surrounded by acute and chronic inflammatory reaction and some hemorrhage. There were patches of degeneration throughout. The fibrous tissue was increased in amount, and infiltrated with polymorphonuclear leucocytes and round cells.

Liver.—Weight, 1,240 grams. The contour was normal. The capsule was smooth and intact. The parenchyma was friable and brownish yellow. On cut section, the architecture was seen to be distorted by yellowish-gray, slightly elevated areas in the central zones of the lobules. Microscopic examination showed evidence of widespread parenchymal injury. There were atrophy, degeneration, and extensive necrosis of the liver cords. These changes were most marked in the central zones, but in many places the injury extended to the midzonal and portal areas. Fatty metamorphosis was present. Large amounts of lipochrome and hemosiderin-like pigments were seen. Islands of regenerating hepatic cells caused distortion of the architecture. There was no increase in fibrous tissue. Numerous round cells and a few large mononuclears were scattered throughout. In many places, these cells formed small nests in the areas of degeneration. Evidence of proliferation of the bile ducts was occasionally seen.

Gall Bladder and Ducts.—The gall bladder was normal in size and contained about 15 c.c. of clear, viscid bile. The mucosa was smooth, but the wall was moderately thickened and opaque. The ducts were patent. Histologically, the submucosa and muscularis of the gall bladder were seen to be edematous and infiltrated with small round cells and polymorphonuclear leucocytes. There was considerable fibroblastic proliferation.

Adrenal Glands.—Grossly, the glands appeared to be normal. Microscopically, there were slight autolysis of the cortex and some cortical atrophy. Occasional small nests of lymphocytes were noted.

Kidneys.—Each kidney weighed 210 grams. They were similar in appearance. The capsules stripped with ease, revealing smooth, pale, yellow surfaces over which were scattered many yellow nodules, varying from 1 to 2 mm. in diameter. Petechiae were abundant. The cortices measured 6 to 7 mm. in thickness. The architecture of the cortices was distorted in areas and obliterated by yellowish-gray streaks and numerous petechiae. The pyramids were well demarcated. From the area cribrosa, numerous yellow-gray streaks, similar to those in the cortices, ascended through the pyramids and caused considerable distortion of structure. The pelvic fat was abundant. The mucosa of the pelves was smooth and intact but marred by occasional areas of congestion.

Microscopically, there was evidence of diffuse nephritis, with focal areas of chronic granuloma. Many glomeruli were completely fibrosed and hyalinized; others showed crescentic scarring or were filled with erythrocytes. The glomerular lesions were extensive but patchy, and many glomeruli appeared normal. The tubules exhibited evidence of moderate, diffuse degeneration and atrophic changes. The epithelial cells were granular, and there was considerable sloughing of cytoplasm into the lumina. Many nuclei contained early pyknotic changes. In some areas, calcium salts were deposited in the tubular epithelium. The lumina

of many tubules were filled with erythrocytes and hyaline casts. Marked distortion of the architecture was caused by diffuse infiltration of the renal parenchyma with lymphocytes, plasma cells, and large mononuclears. In some areas, there was complete obliteration of normal structure. These inflammatory changes were particularly conspicuous in the cortex. In some sections there was a chronic granulomatous reaction, characterized by small areas of necrosis surrounded by epithelioid cells. No giant cells were seen. In some instances, the granulomatous reaction was intimately associated with small abscesses in which polymorphonuclear leucocytes as well as chronic inflammatory cells were present. Patchy zones of interstitial fibrosis were noted, particularly in association with the damaged glomeruli. The intima of a few medium-sized arteries was moderately thickened and hyalinized, but the walls of most vessels, including arterioles, were normal.

Pelvic Organs.—The bladder was contracted, but the wall was normal in thickness. Although the mucosa was smooth and intact, it was marred by granular plaques and several areas of extravasated blood. The prostate gland and seminal vesicles appeared normal. The testicles were normal, but they were embedded in a dense mass of blood extravasated in the scrotal cavity and in the areolar and adipose tissue of the scrotum.

Vascular System.—Throughout its course, the aorta exhibited a moderate degree of atherosclerosis. The walls contained discrete areas of calcification, but no ulceration was noted. The aneurysm of the left femoral artery has been described previously.

Lymphatic System.—The nodes in the pelvis, around the aorta, and near the celiac axis were moderately enlarged and red. Hemorrhages partly obliterated the architecture. Histologically, there was marked hyperplasia of the germinal centers. The endothelial elements were also hyperplastic. The sinusoids were dilated and filled with erythrocytes and large mononuclears. No areas of necrosis were noted.

Brain.—Permission for examination was not granted.

Anatomic Diagnoses.—Brucellosis; bacterial endocarditis (*Br. suis*), with perforation of mitral valve; dissecting mycotic aneurysm of the left femoral artery, with rupture and extension into retroperitoneal tissues; scrotal edema, with intrascrotal hemorrhage; recent and old infarcts of the spleen; diffuse nephritis, with focal areas of granuloma; extensive degeneration and necrosis of the liver; diffuse interstitial fibrosis of the pancreas, with fat necrosis and acute pancreatitis; chronic interstitial pneumonitis; pulmonary emphysema; subacute cholecystitis; and generalized icterus.

BACTERIOLOGIC STUDIES OF TISSUES POST MORTEM

Duplicate cultures were made on blood and tryptose agar plates from the heart valve vegetation, aneurysm wall, blood clot in the aneurysm, lymph nodes, spleen, and liver. One set of plates was incubated in an atmosphere of 10 per cent carbon dioxide, and the other set, under aerobic conditions at 37.5° C. These were examined at intervals of twenty-four, forty-eight, and seventy-two hours. Enormous numbers of *Brucella* colonies were found on the culture plates prepared from the endocardial vegetation, whereas only a few were noted in the other cultures. No colonies of streptococci or other significant organisms were noted on blood agar plates. Blood and tryptose agar plates, incubated under strict anaerobic conditions, failed to show any growth whatsoever.

After the preparation of the initial cultures, portions of the tissues were ground up in individual mortars, and saline suspensions made. Direct smears from the crushed vegetation revealed enormous numbers of pleomorphic, gram-negative bacilli, with the typical morphology of *Brucella*. Organisms were not found in the saline suspensions from other organs by stained smear.

Guinea pigs were inoculated with 0.25 c.c. of saline suspensions of the tissues, with the results noted in Table II. It is interesting that *Brucella* were isolated from the organs of the animals in two instances before the agglutinins appeared in the blood. In one case, *Brucella* agglutinins were absent on the seventh, twentieth, and fifty-eighth days after inoculation, whereas *Brucella* organisms were isolated from the organs of the animal on the twentieth and fifty-eighth days. These observations support the statements in the literature that *Brucella* may be isolated from the human blood prior to the demonstration of agglutinins. In some cases in which the diagnosis was verified by positive blood cultures, agglutinins were not detected throughout the course of the infection. Similarly, evidence of skin allergy may be lacking.

The organisms isolated from the tissues and the blood of this patient grew equally well on tryptose agar under 10 per cent carbon dioxide or under aerobic conditions. The morphology and the staining reactions were typically those of the *Brucella* group. Large amounts of hy-

TABLE II. RESULTS OF INOCULATION OF ANIMALS WITH SUSPENSIONS OF TISSUES

TISSUE FROM AUTOPSY OF PATIENT	GUINEA PIG	DAYS AFTER INOCULATION	GROSS LESIONS IN GUINEA PIG	TITER OF BRUCELLA AGGLUTININS IN GUINEA PIG SERUM	CULTURE FROM GUINEA PIG TISSUES
Spleen	1A	7	No lesions	Negative	Negative
Spleen	1B	20	No lesions	1:20	*Brucella* in all organs
Spleen	1C	35	Small abscesses in liver. Spleen enlarged and containing abscesses. Abscess in groin	1:1,280	*Brucella* in all organs
Spleen	1D	58	Many abscesses in liver. Spleen enlarged and containing many abscesses. Abscess in right groin	1:5,120	*Brucella* in all organs
Liver	2A	7	No lesions	Negative	Negative
Liver	2B	20	No lesions	Negative	*Brucella* in all organs
Liver	2C	35	Small abscesses in liver. Spleen enlarged with abscesses. Abscess in groin	1:10,240	*Brucella* in all organs
Liver	2D	58	Many abscesses in liver. Spleen enlarged. Abscess in groin	1:2,560	*Brucella* in all organs
Endocardial vegetations	3A	7	Many small abscesses in liver	Negative	*Brucella* in all organs
Endocardial vegetations	3B	20	Many abscesses in liver. Spleen enlarged with abscesses	1:640	*Brucella* in all organs
Endocardial vegetations	3C	58	Many abscesses in liver. Spleen enlarged with abscesses	1:10,240	*Brucella* in all organs
Lymph node	4A	7	No lesions	Negative	Negative
Lymph node	4B	20	Few abscesses in liver	Negative	*Brucella* in all organs
Lymph node	4C	58	No lesions	Negative	*Brucella* in all organs
Wall of aneurysm	5A	7	No lesions	Negative	Negative
	5B	20	Many abscesses in liver. Spleen enlarged with abscesses	1:80	*Brucella* in all organs
Wall of aneurysm	5C	35	Many abscesses in liver. Spleen enlarged with few abscesses	1:640	*Brucella* in all organs
Wall of aneurysm	5D	58	Liver normal. Spleen enlarged with abscesses	1:1,280	*Brucella* in all organs

drogen sulfide were produced by the organisms in cultures incubated for five days. The organisms were agglutinated by polyvalent *Brucella* antiserum, and typed as *Br. suis* by the Huddleson bacteriostatic dye method.[18]

SUMMARY

The case of a man with *Br. suis* bacteriemia is reported. The infection lasted approximately two hundred days, during which endocarditis and nephritis developed. He recovered from uremia, only to succumb to rupture of a mycotic aneurysm of the left femoral artery. Sulfonamide therapy and the administration of convalescent serum failed to influence the infection. The pooled serum was prepared from the blood of donors who had recovered from *Br. suis* bacteriemia. Anatomic studies after death revealed, among other things, ulceration and vegetations on a previously normal mitral valve. The specific nature of the lesions was proved, during life, by the repeated isolation of *Br. suis* in pure culture from the blood stream, and, after death, by obtaining pure cultures of *Br. suis* from the vegetations from the endocardium, the walls of the mycotic aneurysm, and other tissues. The blood contained specific agglutinins, but the skin did not react to brucellergin intradermally.

So far as we are aware, this is the first reported case in which ulcerative endocarditis has been proved, beyond doubt, to be due to *Br. suis*. It is the second reported instance in which rupture of a mycotic aneurysm due to *Br. suis* has caused death.

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Clinical Reports

INTRACARDIAC FOREIGN BODY

Report of a Case With Recovery

Lieutenant Robert Shapiro, Medical Corps, U.S.N.R.

THE advent of the war has tremendously increased the incidence of traumatic wounds of the thorax due to various types of missiles It is only natural, therefore, to expect that this increase should also be reflected in the more frequent occurrence of penetrating wounds of the heart. This case is being reported because of the unusual type of wound and the successful recovery of the patient.

CASE REPORT

J. L., a 21-year-old white radioman, was aboard a small boat that was patroling the waters off the coast of New Guinea. On Nov. 11, 1943, at approximately 11 P.M., the lookout sighted two Japanese barges along the shore line, and the order to close in for attack was given. As they were approaching the barges, a Japanese battery, concealed on the beach, opened fire. The patient was standing erect with his arms slightly elevated and forward. During the melee, he was struck by several pieces of ricocheting shrapnel. He felt no severe pain at the time of the injury, but did experience a dull, constricting, nonradiating ache in the right side of the chest along with some dyspnea. He was given first aid treatment by the pharmacist's mate aboard, and was taken to an Army Field Hospital eight hours later.

At the time of admission, the patient was obviously in shock. There were shrapnel wounds of the lateral aspect of the right arm, some in the region of the right iliac crest, and one in his back on the right side near the angle of the scapula. Physical examination revealed diminished expansion, flatness to percussion, and absent breath sounds over the right lung. X-rays of the chest showed a hemopneumothorax on the right side, with considerable displacement of the heart and mediastinum to the left. A metallic foreign body superimposed upon the cardiac shadow was also noted.

The patient was treated vigorously for shock by repeated intravenous infusions of whole blood and plasma. He was also given oxygen and 1 Gm. of sulfadiazine three times a day. Several aspirations of the right pleural cavity resulted in the removal of large quantities of dark, blood-stained fluid and gradual re-expansion of the collapsed lung. The patient's condition steadily improved, and, on Jan. 15, 1944, he was transferred by plane to a Naval hospital facility for further study.

Upon admission at the latter institution physical examination disclosed a well-developed, pale, young adult in fairly good condition but somewhat tired from the plane trip. His temperature was 98.6° F.; pulse rate, 96; respirations, 18; and blood pressure 116/90. Systemic review revealed the following positive and cogent findings. There was a mild acne vulgaris eruption on the face. Several small, well-healed, nontender, irregular scars were noted along the lateral aspect of the upper portion of the right arm. Two similar, well-healed scars were observed just below the right iliac crest, and an erythematous, circular, tender scar approximately ½ inch in diameter was noted over the fourth rib posteriorly on the right side just below the angle of the scapula. The cardiac sounds were of good quality. There was a slight sinus arrythmia. The second pulmonic sound was slightly more accentuated than the aortic second sound. There were no murmurs, thrills, or friction rub audible. Physical examination of the chest was essentially negative.

Laboratory study showed the following: erythrocytes, 4,200,000 per cubic millimeter; hemoglobin, 13 Gm.; leucocyte count, 6,600, with 65 per cent mature segmented polymor-

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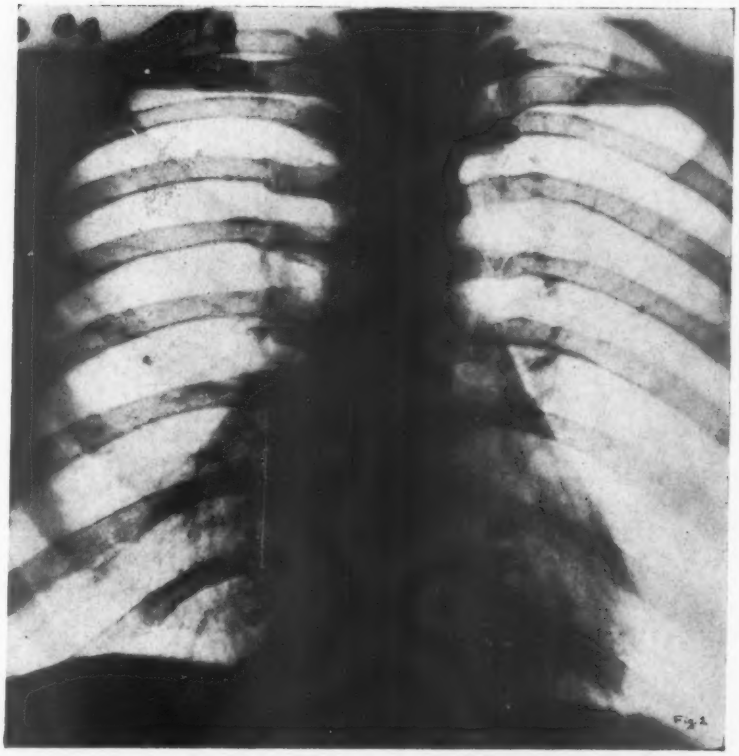

Fig. 1.—Posteroanterior view of chest showing foreign body superimposed upon the cardiovascular silhouette.

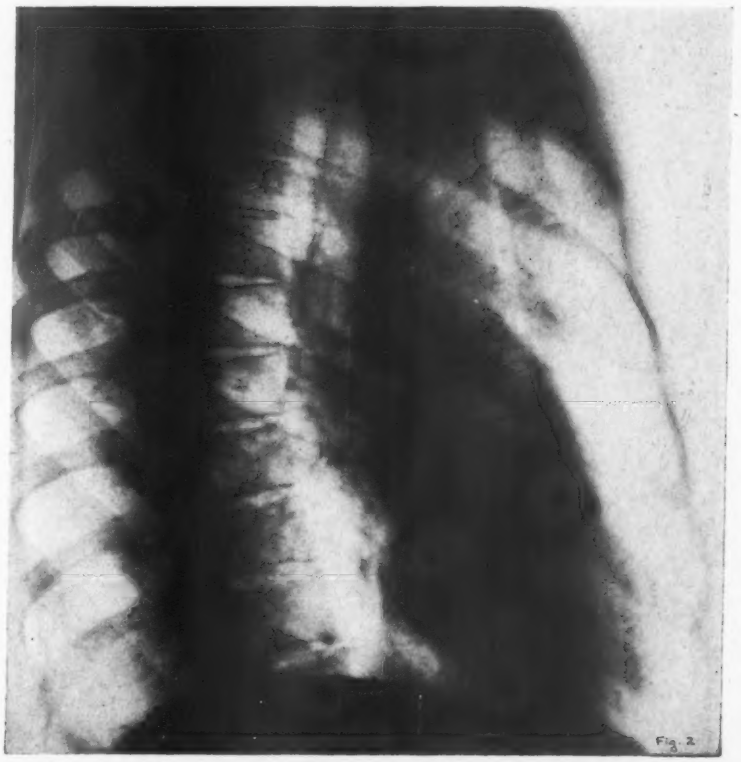

Fig. 2.—Right anterior oblique view showing the foreign body to be in the region of the conus arteriosus of the right ventricle.

Fig. 3.—Left anterior oblique view.

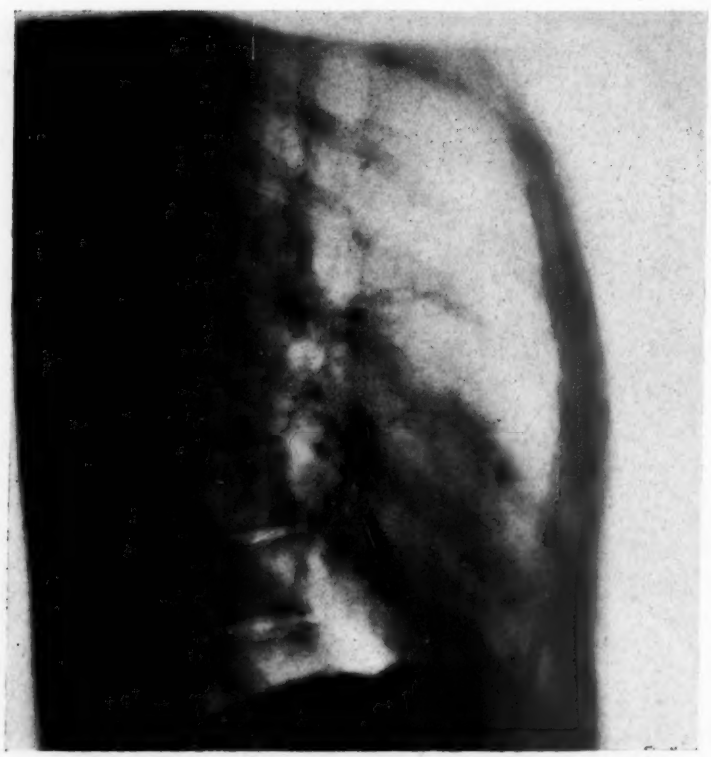

Fig. 4.—Left lateral view.

phonuclear leucocytes, 5 per cent nonsegmented neutrophiles, 25 per cent lymphocytes, and 4 per cent monocytes. Urinalysis: specific gravity 1.020; albumin, negative; sugar, negative; and microscopic examination, 3 to 5 calcium oxalate crystals per high-power field.

Radiographic and fluoroscopic studies showed a rectangular metallic foreign body fragment, approximately 1 by 0.6 cm., embedded in the wall of the right ventricle in the region of the conus arteriosus. This fragment pulsated synchronously with the conus arteriosus and remained fixed when the patient was shifted into prone and lateral decubitus positions. There were also three small metallic foreign body fragments in the soft tissue on the right side below the level of the diaphragm. The fourth rib on the right side posteriorly near the axillary line was fractured. This represented the site of entry of the shrapnel fragment in the heart.

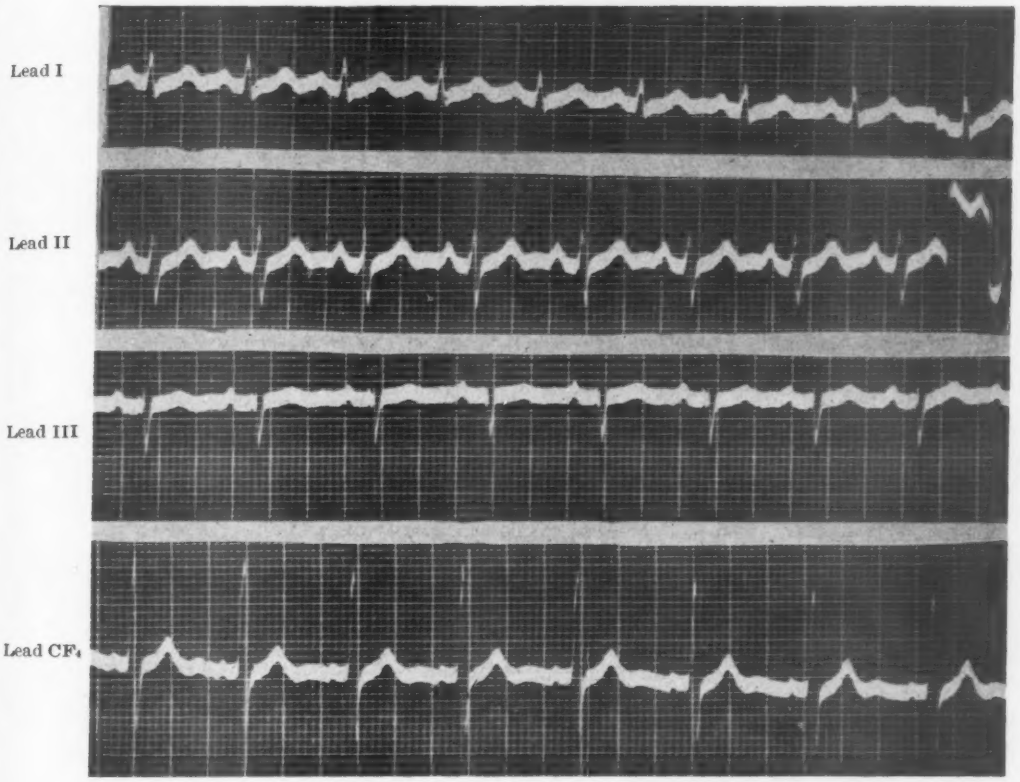

Fig. 5.—Electrocardiogram, taken Jan. 8, 1944, showing low voltage of QRS, left axis deviation, and slight sinus tachycardia (patient of sthenic habitus).

An electrocardiogram disclosed no abnormalities except a slight sinus tachycardia, low voltage of the QRS complex in Lead I, and left axis deviation; auricular rate, 100; ventricular rate, 100; P-R interval, 0.12 second; and QRS, 0.08 second. Leads CF_1, CF_2 and CF_4 were normal.

At the present time, the patient is entirely well clinically and has no cardiac symptoms or signs.

TRANSIENT HEART BLOCK IN CONGENITAL HEART DISEASE

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IN THE presence of congenital heart disease, heart block may be present as a functional part of the congenital defect or may occur as an acquired disturbance, superimposed upon the congenital deformity. The heart block may be complete or incomplete, transient or permanent. In the young, with recent acquisition of this defect in the absence of a history of infection such as syphilis (congenital or acquired), diphtheria, rheumatic fever, or chorea, and in the absence of overdigitalization, the causative factor producing the block is probably related somehow to a congenital defect. Vagal influence must be excluded.

Congenital heart block has been described many times and reviewed several times. Lampard[1] summarized thirty-one cases and reported one case. In many of the cases reviewed, attacks of syncope occurred. Later, Yater, Lyon, and McNabb[2] reviewed forty-four accepted cases of congenital heart block. The occurrence of syncopal attacks at an early age is accepted as good evidence of congenital heart block. These are, however, rare. Both of these reviews are concerned with cases of congenital heart block, *not* acquired *after* birth in the presence of congenital defects, but believed to have been present since birth.

Parkinson, Papp, and Evans[3] collected and reported fifty-six cases of Stokes-Adams attacks with electrocardiograms taken during the attack and added eight more cases. They define Stokes-Adams disease as a name applicable to the condition of patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these. In a true Stokes-Adams attack, the auricle continues to beat. In all, they found twenty-eight cases of Stokes-Adams disease with ventricular standstill and added five of their own. One patient was 16 years of age; the remaining varied in age from 29 to 78 years. The diagnosis of the underlying cardiac condition was not given in all cases. None were stated to have a congenital basis. They state that "no actual electrocardiogram of Stokes-Adams attack in congenital heart block has been found." Faessler[4] collected eight cases of Stokes-Adams attack in congenital heart disease. Six cases had complete heart block between attacks. Six were diagnosed as patent interventricular septum, one as patent ductus arteriosus, and one as persistent foramen ovale. In Faessler's[4] added case, there was no true heart block, but nodal rhythm was present during the period of unconsciousness. Between attacks the pulse rate was 120 to 140, with a normal electrocardiogram. The first attack occurred when the patient was 6 months old. During the attack, the pulse rate dropped to 22 and the electrocardiogram showed a nodal rhythm. In the other reported cases, auriculo ventricular block was present. Autopsy on Faessler's[4] case showed transposed large vessels, double aortic arch, pulmonary stenosis, subaortic defect in the interventricular septum, and patent foramen ovale. The connecting auriculoventricular tissue was normal. However, there was intimal thickening on the main artery of the sinus node.

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Physiopathology of Stokes-Adams Attacks in Congenital Heart Disease.—Septal defect is usually assumed to be present in the presence of congenital heart block. Fleming and Stevenson[5] feel that the presence of heart block in congenital heart disease is an important sign, indicative of a defect in the posterior part of the interventricular septum. Leech[6] described a case of congenital complete heart block associated with a patent ductus arteriosus where the possibility of a patent interventricular septum was not ruled out, but this was considered possible because of the presence of congenital complete heart block. This deduction is not fully justified as will be noted from the evidence to be presented. It is true that septal defect is the commonest deformity associated with heart block, yet, although a patent interventricular septum is the commonest congenital cardiac defect, congenital heart block is rather rare. This is probably due to the fact that the A-V bundle usually is behind the pars membranacea, while the defect is usually anterior. In instances where the defect is large, heart block may be absent. Lampard[1] correctly stated that patency of the septum is not the sole cause of the heart block. We know that as long as bundle fibers are present, though decreased in number, they may conduct an impulse. Theoretical physiologic considerations have been offered to explain the reasons for fluctuations in the conductivity of the bundle. These considerations relate to pressure, tension, or circulatory changes affecting the bundle and interfering with its conductivity.

a. Pressure and Tension Variations on the Bundle: Wilson and Grant[7] found microscopically in a case of two-to-one heart block that dense fibrous tissue, instead of normally encircling the A-V bundle, had penetrated into the fibers of the bundle and had separated them into fine strands. They state "it is not difficult to imagine the fine strands being subjected to unusual pressure, especially in view of the circulatory failure shown by the patient during life." In the three cases studied microscopically by Yater, Lyon, and McNabb,[2] the A-V bundle showed imperfect development. Nisse,[8] reporting a case of congenital heart block in a patient 1 year, 11 months old, noted that "slight variations in the degree of pressure on the bundle will probably account for the fact that in the case described the heart block is at times 2:1 and at other times complete." Lewis[9] reported that alterations in tissue tension might abolish conduction in a bundle where it already was precarious. He described a case of heart block that developed suddenly in a woman in whom large venous sinuses separated the A-V bundle fibers. He attributed the attacks to intermittent swelling of the sinuses which interrupted conduction transiently by pressure. Smith[10] described a 20-year-old man with congenital heart block. The electrocardiogram showed complete heart block except in forced expiration, when there was none. In this case, the heart was more horizontal in forced expiration and more vertical on inspiration. The decreased tension on the bundle during expiration supposedly released the blocking of impulse transmission. Calandre[11] presented a case with complete dissociation except in complete repose, when there was normal conduction. It is not unreasonable to suppose that an incomplete or variable dissociation could be due to slight variations of pressure on a tract, the tissues of which are abnormally surrounded or interrupted by fibrous tissue; the block varies with the tissue tension on the bundle strands. Brown[12] stated "it appears likely that for reasons of strain, heart block may be acquired in a congenital lesion."

b. Circulatory Variations Causing Block: Faessler's[4] case, on microscopic study, revealed thickening of the intima of the main artery to the sinus node.

The Stokes-Adams attacks were attributed to marked decrease in blood circulation (during exertion) to the sinoauricular node due to the narrowed lumen, so that stimulus formation slowed down and the A-V node took over the function of pacemaker. Comeau[13] summarized twelve cases and presented one additional case of attacks of complete A-V block with Stokes-Adams syndrome, alternating with normal rhythm. The patients varied in age from 43 to 78 years, and none had congenital heart disease. Comeau's patient later developed complete block, and the syncopal attacks disappeared. His conclusion regarding the mechanism of block production is that most cases are due to arteriosclerosis with some bundle damage. The fluctuating character of the conduction probably is determined by temporary variations in local circulation to the remaining intact fibers.

Whether symptoms develop during transient block, and what the severity of these symptoms will be, is dependent upon the duration of the circulatory arrest. However, other important factors are: the rapidity of onset of the block, the extent of decrease in rate, the blood pressure, the presence of anemia, the oxygen saturation of the blood, and the condition of the cerebral arteries. Symptoms are most apt to occur when complete heart block is interrupted by ventricular asystole of sudden onset, or when block occurs suddenly in the presence of normal rhythm.

Fleming and Stevenson[5] stated that in the absence of gross cardiac abnormalities, the block per se causes little or no disability. They felt that most symptoms such as cyanosis, dyspnea, and syncopal attacks could be accounted for by the extent of the cardiac deformity, rather than on the degree of block. This opinion is not confirmed by a study of the literature where stress is laid on the point that a sudden increase in block, a slowing of the ventricular rate of sudden onset, or sudden appearance of block may cause Stokes-Adams attacks with syncope.

Leech[14] stated that in a patient with congenital heart disease, and in the absence of causes such as pneumonia, epilepsy, meningitis, and severely toxic conditions, the occurrence of convulsive-like or epileptiform seizures may be interpreted as indicative of a lesion permitting a venous shunt. It is true that in infants, exertion and crying can cause convulsions and cyanosis in the presence of such a lesion. I should like to add transient heart block as another possible cause of similar symptoms in patients with congenital heart disease.

The case presented here is one of congenital heart disease, the lesion of which is clinically characteristic of patent ductus arteriosus, with no other evident associated lesions. Transient episodes of heart block occurred interrupting a normal rhythm. These episodes were associated with mild attacks of Stokes-Adams syndrome. A so-called typical electrocardiogram of congenital heart disease and the electrocardiogram of the block are presented, during the filming of which the patient fainted several times.

CASE REPORT

S. S., a man, aged 18 years, was known to have been born with "heart trouble." He had never been called a blue baby and never was known to have suffered cyanosis either at rest or on exertion. At school, he had always attended the cardiac classes and was restricted physically. He terminated his education after the seventh term in high school in order to go to work. There was no history of rheumatic fever, chorea, diphtheria, or congenital or acquired syphilis. He had always been capable of moderate exertion without dyspnea. He had no precordial pain, and no peripheral edema. The one symptom of which this patient was aware was a strong heartbeat, which often annoyed him as he

heard it pounding on his pillow at night. At the present time (November, 1942), he was employed as a shipping clerk in a dress factory.

On Nov. 22, 1942, a regular physical examination disclosed the following: A poorly nourished, underdeveloped white man, aged 18 years, 64 inches in height, and 96 pounds in weight. He was not acutely ill. There was no cyanosis or clubbing of the fingers or toes. There was no dyspnea. Eyes, ears, and nose were normal. Tonsils were neither enlarged nor infected. No cervical adenopathy was present. There was a marked increase in the pulsation of the neck vessels with a palpable systolic thrill.

Thorax: There were marked asymmetry of the chest, with precordial bulging, and narrowing of the intercostal spaces in the left axilla and posteriorly, while the spaces widened anteriorly. Systolic precordial interspace retraction was plainly visible. Marked kyphoscoliosis was present. The lungs percussed resonant except at the left base, where resonance was diminished. At this same area, bronchovesicular breath sounds were heard. The heart was markedly enlarged. The apex was felt in the sixth left intercostal space at the anterior axillary line. The entire precordium heaved with systole, while the strong apical thrust was felt separately. A fine systolic thrill was palpable over the second and third left intercostal spaces, adjacent to the sternum, which was transmitted into the cervical vessels. A short diastolic thrill was also felt in the second and third left intercostal spaces. On deep inspiration, these thrills disappeared. The area of cardiac dullness was outlined on percussion as follows:

	Right (cm.)	Left (cm.)
II	3.5	6.5
III	4.0	9.5
IV	3.5	14.0
V	3.5	15.0
VI	3.5	16.0

A loud systolic blowing murmur was heard over the entire chest, anteriorly and posteriorly, with greatest intensity over the second left intercostal space, then at the third left intercostal space and down the left sternal border. The pulmonic second sound was accentuated, and followed by a short diastolic murmur at the second left intercostal space. The systolic blood pressure was 150. At 40 mm. Hg a change in the character of the sound was heard, but thumping sounds could be distinguished down to the zero reading. A pistol shot could be heard in the groin, but Duroziez's sign was negative.

The abdomen showed nothing of note.

A circulation time with decholin gave an arm to tongue time of 13 seconds, which spoke against any veno-arterial shunt.

Fluoroscopy revealed marked cardiac enlargement with a very prominent, dilated pulmonary artery which showed exaggerated pulsations, filling synchronously with ventricular systole. The hilar "dance" was present. The transverse diameter of the heart measured 175 mm. at this time as determined by the rapid method.[15] The blood Wassermann test was negative. The blood picture was normal. No polycythemia was present.

Four days later, on November 26, the patient was brought in. He had had several dizzy and fainting spells within the previous few hours, following undue and unusual exertion at a party where he had danced until 3 A.M. He had been feeling well until then but suddenly noted increased pounding of the heart, and periods where the heart seemed to "jump out of the chest and disappear into blackness." Periodic attacks of giddiness and faintness appeared. Transient periods of unconsciousness had been suffered lasting one minute or less. Because of the irregularity of the heartbeat noted, an electrocardiogram was taken at 6 A.M., three hours after the onset of the attacks.

The electrocardiogram (Figs. 1*A* and 1*B*) revealed the following: In Lead I, the auricles and ventricles follow each other at a regular rate of 100. The P-R interval is 0.16 seconds. At the end of the lead is noted a period of complete asystole, which merges into Lead II. Lead II*A* starts with a complete heart block. The auricular rate is maintained at 100, while the ventricular rate drops to 39. The initial interval between ventricular systoles is 1.6 seconds.

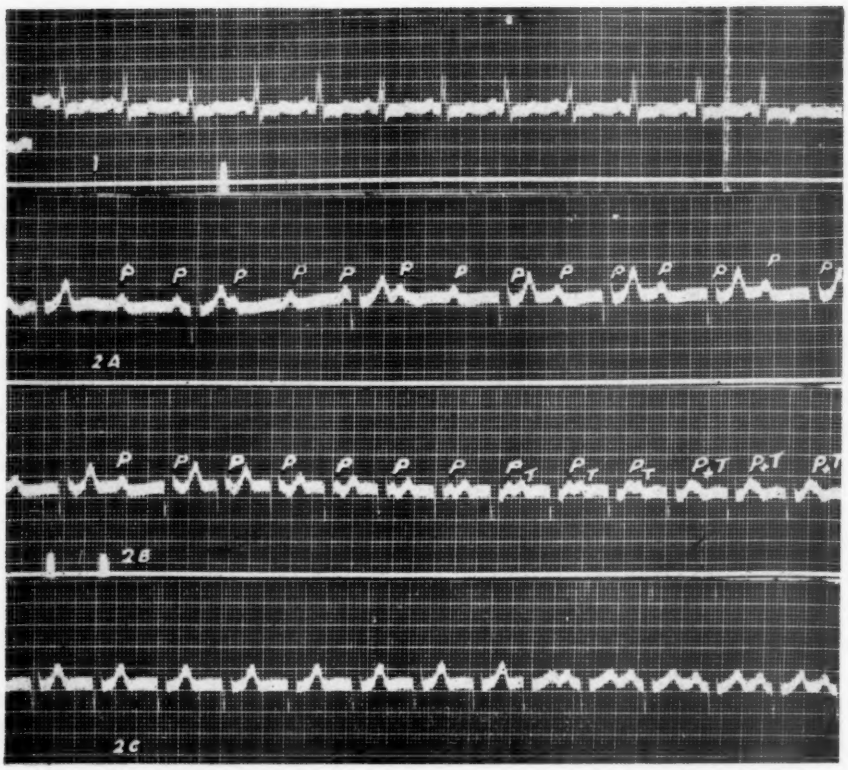

Fig. 1*A*.—Varying degrees of heart block in congenital heart disease. See explanation in text.

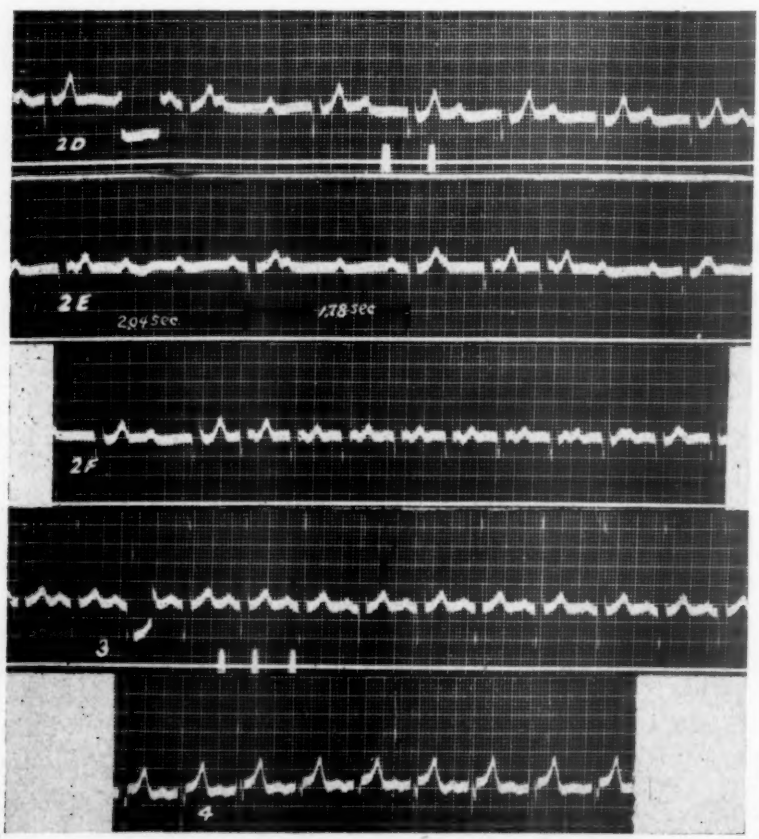

Fig. 1*B*.—This is a continuation of the electrocardiogram in Fig. 1*A*. See explanation in text.

In the second half of Lead II*A*, the ventricle spontaneously increases its rate to 63, while the auricle continues at 100. In II*B*, the auricle increases to 115, while the ventricles increase their rate to 100, each independent of the other. In II*C*, the P and T waves merge, then separate. The first half of this lead appears as a prolonged P-R interval of 0.28 seconds with P and T merging, while the latter half shows no block, the P-R interval being 0.18 seconds with a sinus tachycardia of 100 being present. In II*D*, we see a complete heart block followed by a two-to-one block, with the auricles at a rate of 110 and the ventricles at a rate of 55. The P is buried in the base of the descending limb of R. In II*E*, complete heart block is evident with periods of ventricular asystole of 2.04

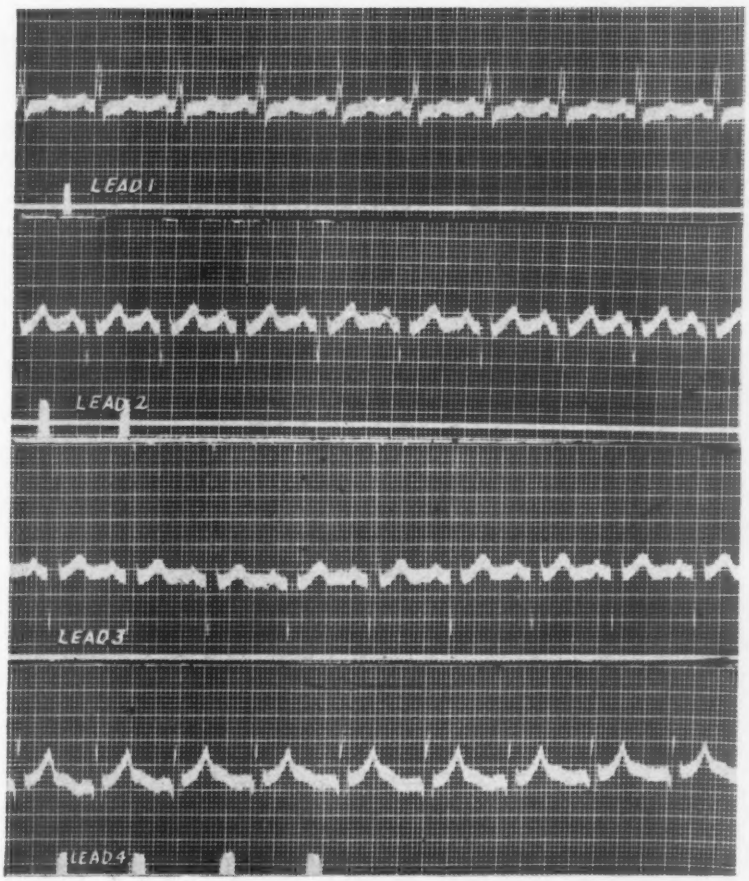

Fig. 2.—So-called typical electrocardiogram of congenital heart disease. Normal rhythm.

and 1.78 seconds. In II*F* there is complete dissociation, with a rapid ventricular rate of 110. During the filming of Lead II the patient fainted for several seconds, and periods of light-headedness with sensations of faintness recurred. The attacks resembled those of petit mal. He constantly shook his head to throw off the sensation of faintness. No twitchings were observed. These were mild attacks of the Stokes-Adams syndrome. In Leads III and IV, there is a return to sinus tachycardia at a rate of 100 with a P-R interval of 0.16 second. It is to be noted in Lead II*F* that complete dissociation exists with a rapid ventricular rate of 110. This is not uncommon in childhood where complete dissociation may exist with a rapid rate.[6, 12]

A fluoroscopic examination was then made which revealed a transverse cardiac diameter of 185 mm. by the rapid method,[15] indicating an enlargement of 10 mm., over the measurement taken four days previously. An injection of $\frac{1}{100}$ grain of atropine sulfate was given at this time. It had no effect on the recurrence of the fainting spells which continued for the next few hours. This indicated that the attacks were not due to a vagal influence. Ephedrine sulfate, $\frac{3}{8}$ grain, was given every three hours. Following the first dose two attacks occurred, but none appeared since then.

An electrocardiogram taken on November 30 (Fig. 2), showed a regular sinus tachycardia at a rate of 100. The P-R interval was 0.16 second. The widest QRS is 0.10 second, and is notched and slurred in Lead I. The diphasic character of QRS in Leads II and III are pathognomonic of congenital heart disease.[16] Katz[16] described such findings as being indicative of congenital defects in the septal conduction system, although in the case here presented,

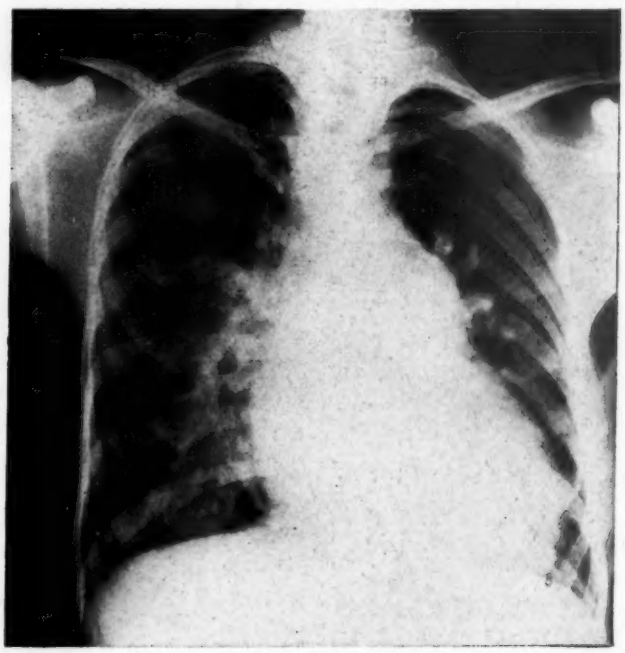

Fig. 3.—Patent ductus arteriosus. Anteroposterior view.

there is no definite clinical evidence of a septal defect. The possibility of some imperfect development in the bundle fibers must be considered. Fluoroscopy at this time revealed a return in transverse diameter of the heart to 175 millimeters.

An x-ray (Fig. 3) taken on Dec. 2, 1942, was reported as follows: A markedly enlarged heart with diminished prominence of the aortic knob, marked prominence of the pulmonic curve, straightened left cardiac contour, and accentuation of the left ventricular curve. The measurements were: transverse diameter, 16.4 cm.; broad diameter, 13 cm.; long diameter, 18.3 cm.; transverse diameter of the chest, 26.2 cm.; and the cardio-thoracic ratio was 63. The angle of obliquity was 45 degrees. The pulmonary fields showed marked engorgement of the lesser circulation. In the right oblique view (Fig. 4) the arrow points to the pulmonary artery as seen on edge, with increase in

size evident. The dilated branches of the pulmonary artery are plainly visible. These findings agree with those of Donovan, Neuhauser, and Sosman[17] in patent ductus arteriosus.

It becomes evident that heart block of varying degrees occurred following exertion. At the time of block, the heart diameter showed some widening transversely from 175 to 185 mm. (by the rapid method[15]) on fluoroscopy, evidently a dilatation. It is possible that during and following exertion, the increase in return flow of blood to the heart may have increased the pressure on the bundle of His which, with increase in the size of the ventricle, added tension to the bundle which varied in degree and caused a varying degree of heart block.

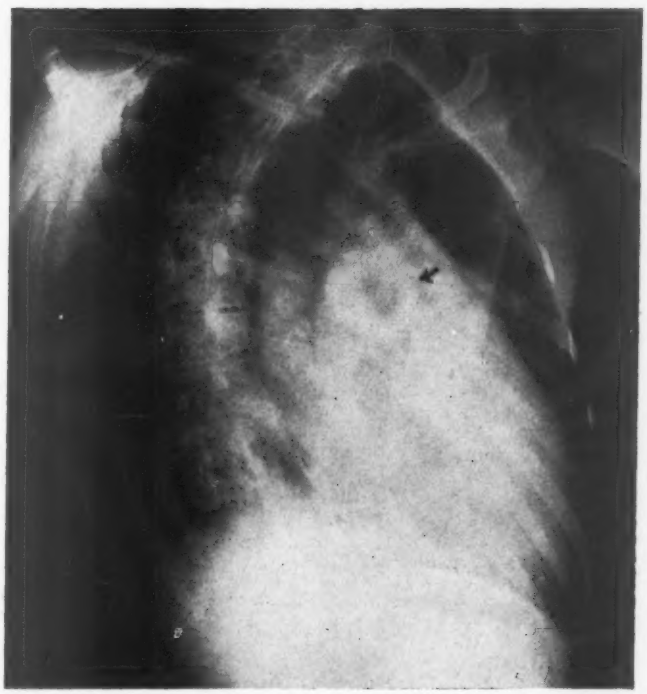

Fig. 4.—Patent ductus arteriosus. Right oblique view. Arrow points to pulmonary artery seen on end.

Whether the bundle is anatomically defective is not known. It is possible that there is a fibrous tissue disturbance interfering with conductivity. It is of interest to note Lampard's[1] statement that where heart block, murmurs, and enlargement are present "great caution should be enjoined and no games or violent exertion permitted" although each case must be judged individually. It is advisable to re-emphasize this enjoinder that undue exertion be interdicted in the presence of congenital heart disease, whether or not heart block is present.

SUMMARY

Varying degrees of heart block may occur in the presence of congenital heart disease, and cause mild Stokes-Adams attacks which conceivably could be more severe, with convulsions. The symptoms then are not due to the congenital heart disease but to the cerebral anoxia that follows the ventricular standstill. This condition may occur in congenital heart disease where no evidence of an interventricular septal defect is apparent.

A case is presented with definite evidence of a patent ductus arteriosus, and no evidence of a patent interventricular septum, in which mild Stokes-Adams attacks occurred associated with the sudden onset of heart block, which varied in degree, was transient and followed by normal rhythm. This occurred following exertion, and was not of nervous origin. This is the first case to be reported of congenital heart disease with Stokes-Adams attacks in which an electrocardiogram taken during the attack is presented.

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Abstracts and Reviews

Selected Abstracts

Shipley, R. E., and Gregg, D. E.: The Cardiac Response to Stimulation of the Stellate Ganglia and Cardiac Nerves. Am. J. Physiol. **143**: 396, 1945.

In confirmation of previous work, faradic stimulation of either the stellate ganglion or its cardiac branches in the anesthetized open-chest dog causes a considerable and sustained increase in coronary flow. Measurements of cardiac input and oxygen utilization have demonstrated that cardiac work and metabolism are also increased.

The cardiac nerves arising from the stellate ganglia are believed to be primarily involved in a mechanism by which the work output of the heart may be increased by nervous control. The promptness of the cardiac response and the somewhat prolonged aftereffect suggest the elaboration of a cardiac stimulating substance at the endings of the stimulated nerves.

The failure to obtain an increased coronary flow response without evidence of increased cardiac vigor, work, or metabolism, the lack of conclusive evidence that the cardiac nerves have a direct vasomotor influence, and the observation that cardiac metabolism is considerably increased, all lend support to the thesis that the increase in coronary flow may be largely, if not entirely, a secondary phenomenon. The increased vigor of cardiac contraction and the associated increase in cardiac metabolism resulting from nerve stimulation are regarded as the primary effects which indirectly give rise to coronary vasodilatation by (1) increasing locally the production and elaboration of metabolites, and/or (2) by creating a local relative anoxia caused by a disproportion between the increased rate of oxygen utilization and the existing coronary blood flow.

The role played by the cardiac nerves arising from the stellate ganglia is believed to be one associated with the adaptation of the work output of the heart to the blood flow and pressure requirements of the whole animal and not primarily one of coronary vasomotor adjustment to the requirements of the heart. AUTHORS.

Moritz, A. R., and Weisiger, J. R.: Effects of Cold Air on the Air Passages and Lungs. Arch. Int. Med. **75**: 240, 1945.

In this investigation, dogs were caused to breathe extremely cold air for periods ranging between twenty and one hundred thirty-three minutes. The rate at which air was warmed within the body was measured by means of appropriately placed thermocouples. The air was delivered to the larynx at temperatures which ranged between -50° and -28° C., and in no instance were temperature records lower than +18° C. observed at the bifurcation of the trachea.

The inhalation of cold air in circumstances such that intralaryngeal inspiratory nadirs as low as or lower than -30° C. were reached resulted in the development of a localized sublaryngeal tracheitis. In some animals the disturbance was limited to unusual activity on the part of the mucus secreting glands, and in others there was focal destruction of the superficial epithelium. In no instance was there evidence of primary injury to the lower portion of the trachea, the bronchi, or the lungs.

The aspiration of mucus or mucus and mucosal detritus from the upper portion of the trachea may result in the development of small and evanescent foci of pulmonary emphysema and atelectasis.

The explanation of the rapid warming of inhaled cold air and of the occurrence of relatively mild and localized injury following the inhalation of cold air lies in the fact that dry air has an extremely low heat capacity and that the number of calories required to produce a great rise in the temperature of dry air can be provided by the heat derived from the cooling of a small amount of tissue by a few degrees.

Although the intermittent exposure to cold air that occurs during normal respiration does not cause significant injury to the pharynx or larynx, a continuous exposure of these structures to cold may result in the development of a rapidly obstructive edema.

Experiments on dogs warrant the inferences (a) that it is unlikely that significant injury to the air passages of man would result from the breathing of air at any degree of coldness likely to be encountered in nonexperimental conditions so long as it was inhaled through the nose or between partially closed lips, and (b) that even though extremely cold air were inhaled rapidly through a widely opened mouth, it would be warmed to a point well above freezing by the time it reached the bronchi. AUTHORS.

Dawson, P. M., and Hellebrandt, F. A.: The Influence of Aging in Man Upon His Capacity for Physical Work and Upon His Cardio-Vascular Responses to Exercise. Am. J. Physiol. **143**: 420, 1945.

Observations on the capacity for physical work and the cardiovascular reactions during exercise were made upon a single subject. The latter rode a cycle-ergometer at 41, 53, 57, 68, and 71 years of age. During these rides the arterial blood pressures and pulse rate were usually determined, and the external work done was calculated for each ride. The results obtained support the following conclusions.

With age, working capacity fell off, becoming, at 71 years, about 50 per cent of what it had been at 41 years. When two rides are performed on the same day the score in the afternoon is greater than the score in the morning by about 3.5 per cent at both 57 and 68 years. The number of days necessary for complete recovery from a ride is greater at 68 and 71 than at 57 years of age. The circulatory reaction during maximal performance is much the same at all these ages. At 41 years the systolic pressure rose higher, but the ride which produced this pressure was only two-thirds as long as the rides performed later, and the tempo was much higher. The resting values of the systolic pressure whether lying or sitting on the cycle-ergometer did not change between 41 and 68 years of age. The maximum reduction of the resting pulse rate due to training is about the same at 41 and at 71 years. In training for a test on the cycle-ergometer the best preparation is to ride frequently upon this apparatus or to perform 3-mile runs. Road walking and mountain climbing do not yield as good results. AUTHORS.

Sabathie, L. G., and Gaspary, F. V.: Unstable Auriculoventricular Heart Block, Permanent, Residual and Benign. Rev. argent. de cardiol. **11**: 215, 1944.

An electrocardiographic study was made of four cases of unstable A-V blocks: a disturbance characterized by the mixture in variable proportions of high grades of partial A-V block with periods of complete block. The necessary conditions for the production of this type of A-V block are: (a) the lengthening of the postsystolic period of inexcitability due to the prolongation of the refractory period of the A-V node or bundle of His which determines at least a two-to-one partial A-V block; (b) a sinus rhythm of normal or slightly subnormal frequency and, in case of sinus tachycardia, a higher grade of A-V partial block; (c) a low ventricular rate as a result of the above mentioned conditions favoring the eclosion of an idioventricular rhythm of similar or slightly faster rate.

The cases reported are classified as unstable, permanent, residual, and benign A-V block. They are permanent, because they are unaltered during long periods of observation (two to fifteen years); residual, because no acute disease, intoxications, or organic heart disease could be found as a cause, the supposition being made that they are the result of a minimal myocardial alteration produced in the course of diverse minor pathologic processes; and benign, because they constitute the only manifestation of heart ailment, and have no evolutive tendency or grave repercussion on the circulatory capacity. AUTHORS.

Goldberger, E.: The Basic Electrocardiographic Patterns in Bundle Branch Block. J. Lab. & Clin. Med. **30**: 213, 1945.

When unipolar leads are used, the electrocardiographic patterns observed in cases of bundle branch block may be directly correlated with the actual spread of the impulse through the ventricles. On the basis of theoretical considerations and actual electrocardiographic observations, the following are the basic electrocardiographic patterns in cases of bundle branch block:

1. An M-shaped QRS complex in unipolar leads overlying or facing the affected ventricle and the affected side of the interventricular septum.

2. A W-shaped QRS complex from unipolar leads overlying or facing the contralateral normal ventricle and the normal side of the septum.

3. Prolongation of the QRS interval to 0.11 second or longer.

4. A negative T wave with the M-shaped QRS and a positive T with the W-shaped QRS, although exceptions to this are frequent.

5. The patterns observed with unipolar extremity and standard leads depend on the position of the heart. When the heart is vertical, the left leg lead will face the left ventricle and the left side of the septum. When the heart is oblique or horizontal, the left arm lead faces the left ventricle and the left side of the septum, and the left leg lead tends to face the right ventricle and right side of the septum.

Not every case in which the QRS interval exceeds 0.11 second is due to bundle branch block. In such cases the widening of the QRS interval is due to the fact that the impulse requires a longer time to penetrate a greatly hypertrophied ventricle than it normally needs.

AUTHOR.

Burrett, J. B., and White, P. D.: Large Interauricular Septal Defect With Particular Reference to Diagnosis and Longevity. Am. J. M. Sc. **209**: 355, 1945.

Interauricular septal defects, which measure 1 cm. or more in diameter in individuals over 8 months of age, are of clinical significance and occur more frequently than do other congenital cardiovascular anomalies. Lesser defects are silent except in rare instances where they may permit the passage of small emboli from the right to the left auricle.

To avoid confusion as to the location of an interauricular septal defect, the suggestion is offered that it be described as being situated in the upper, middle, or lower portion of the interauricular septum.

A clinical analysis is presented of comparative studies in sixty-two autopsied interauricular septal defect cases collected before 1934 (by Roesler) with thirty-one autopsied interauricular septal defect cases collected since that date. There appears to be no definite sex preference. The size of the lesion beyond 1 cm. does not influence its symptomatic course or the longevity. Complicating mitral stenosis, except for occasionally associated auricular flutter and fibrillation, does not alter the picture after adulthood is reached. In a majority of cases, the patient is only mildly disabled from dyspnea and may withstand the ordinary physical and mental wear and tear accompanying the active life for years before succumbing to frank right heart failure. The average age of death lies between 36 and 37 years, and over 50 per cent of persons live beyond 40 years of age. Not uncommonly, individuals may pass the middle age mark without ill effects from this lesion, as demonstrated by Case 2. Complications, other than congestive heart failure, which is at times associated with terminal pneumonia, are conspicuous by their rarity. Only one case complicated by subacute bacterial endocarditis has been reported.

It is conceivable that secondary pulmonary arteriolar disease may develop in certain instances and be responsible for decreasing longevity. Pulmonary vascular lesions (sclerosis and thrombosis) were noted at autopsy in the authors' two cases. In the future, more careful microscopic examination of the pulmonary vascular bed should be accomplished.

The clinical recognition of interauricular septal defect cases has risen markedly in the past decade. A clinical diagnosis of nearly 50 per cent (fourteen of thirty-one cases) has been made since 1933, whereas previously only one in 62 cases was so diagnosed though considered in four other cases. Roentgen-ray investigation, electrocardiography, and a recognition of primary right heart involvement has been chiefly responsible for the recent percentage increase in diagnosis.

A further step in the recognition of these cases will be possible if roentgen-ray and electrocardiographic criteria are evaluated in lieu of certain associated symptoms and signs favoring an interauricular septal defect over pulmonary arteriolar disease as a cause for right heart embarrassment. In the latter instance, cyanosis is an early constant sign, longevity subsequent to the development of symptoms is short, and physical and roentgen-ray findings parallel the clinical course. In the former, mild dyspnea, usually without cyanosis, is an early and outstanding manifestation, and there is little or no disability for several years despite physical, roentgen-ray, and sometimes electrocardiographic findings indicative of rather marked right heart involvement. With these differentiating points in mind, it is believed that the diagnosis in the future will become possible in a much higher percentage of cases.

Left auricular pressure is apparently relieved by the passage of blood through an interauricular septal defect opening to the extent that there is little or no resultant left auricular enlargement despite coexistent mitral stenosis. The roentgen-ray picture remains that of pure right heart involvement. Therefore, mitral stenosis should offer no barrier to the diagnosis of a coexisting defect. On the other hand an interauricular septal defect, by effecting a reduction in the left auricular pressure, frequently results in disappearance of the mitral di-

astolic murmur as well as of left auricular enlargement in cases with mitral stenosis, and thus conceals the latter lesion. This fact is borne out by the discovery of coexisting mitral stenosis in nineteen of thirty-one autopsies in contrast to its clinical recognition in only nine of these cases. AUTHORS.

Finland, M., Parker, F., Jr., Barnes, M. W., and Joliffe, L. S.: Acute Myocarditis in Influenza A Infections. Am. J. M. Sc. **209**: 455, 1945.

Two cases with pathologic findings of acute nonbacterial myocarditis are reported. One of these patients died of cardiac failure and had a minimum of involvement of the lungs; the other died of an extensive acute bronchopneumonia from which no significant bacterial pathogen could be recovered. Influenza A virus was isolated from the lungs in both cases.

A review of the literature concerning the clinical and pathologic aspects of acute myocarditis complicating influenza and similar respiratory infections is presented. The relation of the influenza virus to the cardiac lesions in the present cases is discussed.

It is suggested that the myocardial lesions in these cases are the result of infection with influenza A virus. AUTHORS.

Hamilton, T. R., and Hamilton, B. W.: Pathology and Bacteriology of Streptococcus Endocarditis in Relationship to Sulfonamide Chemotherapy. I. The Development of a Laboratory Technique for the Study of Chemotherapy in Vitro. Am. J. Clin. Path. **14**: 495, 1944.

A simple, workable, laboratory technique for predicting the effect of drugs on organisms infecting the blood stream is presented. Sulfathiazole is effectively bacteriostatic within the therapeutic range, i.e., 406 mg. per cent, in fresh, whole, human blood, for streptococci of Lancefield's Groups A, B, C, and G.

Enterococci, represented by Group D streptococcus, and *Streptococcus fecalis,* were resistant to sulfathiazole in concentrations within the therapeutic range. AUTHORS.

Hamilton, B. W., and Hamilton, T. R.: Pathology and Bacteriology of Streptococcus Endocarditis in Relationship to Sulfonamide Chemotherapy. II. The Effect of Temperature Elevation on the Action of Sulfathiazole Upon Endocarditis Strains of Streptococcus Viridans, Enterococci and Group A Streptococci. Am. J. Clin. Path. **14**: 502, 1944.

These findings lead to the conclusions that the growth of the strains of viridans streptococci and enterococci tested by the method presented were enhanced at 40° C. Chemotherapy with sulfathiazole did not appear more effective at 40° C. than at 37° C. for these organisms, and in some instances it was less effective in whole, human blood as shown by a method that rather strikingly demonstrates the enhanced sulfathiazole effect on Lancefield's Group A, C-203 streptococcus at such elevated temperatures. AUTHORS.

Call, J. D., Beggenstoss, A. H., and Merritt, W. A.: Endocarditis Due to Brucella: Report of Two Cases. Am. J. Clin. Path. **14**: 508, 1944.

Two cases of endocarditis due to *Brucella* organisms have been presented with clinical and pathologic details. Among the peculiarities of this type of endocarditis are the tendency to involvement of the aortic valve, the tendency to ulceration and perforation, and the granulomatous nature of the visceral and neurological lesions noted in Case 2. AUTHORS.

Gubner, R., Szucs, M., and Ungerleider, H. E.: Provocative Prolongation of the P-R Interval in Rheumatic Fever. Am. J. M. Sc. **209**: 469, 1945.

Impairment of atrioventricular conduction of considerable degree was induced in twelve to sixteen subjects with rheumatic carditis by pressure on the carotid sinus. Similar pressure had produced no such impairment in sixteen control cases.

Preliminary administration of prostigmine augments the response in many cases.

The effect is more marked when the P-R interval is initially 0.18 to 0.20 second than when it is less than 0.18 second.

The changes in conduction are maximal during the acute stages of carditis and tend to disappear as rheumatic activity subsides.

It is suggested that this procedure enhances the diagnostic value of prolongation of the P-R interval in rheumatic fever. AUTHORS.

Katz, L. N., Wise, W., and Jochim, K.: The Dynamic Alterations in Heart Failure in the Isolated Heart and Heart-Lung Preparation. Am. J. Physiol. 143: 507, 1945.

In the special heart preparations discussed in previous communications, cardiac failure was studied in twenty-two isolated heart and sixteen heart-lung experiments. The reasons for development of failure when the heart is removed from the body are unknown; failure eventually terminates the experiment. The manifestations of failure are (1) increase of one or both venous pressures without increase in cardiac output, and/or (2) decrease of cardiac output (pulmonary flow) and often also aortic pressure (the latter usually later if at all). Once initiated, cardiac failure pursues an apparently vicious accelerating course with the slopes becoming progressively steeper in their upward or downward trends, and especially when aortic pressure begins to fall the failure accelerates tremendously. All types of failure in the experiments are due to decreased power of the heart, but where the cardiac output and arterial pressures are level and the venous pressure rises on the left and/or right side, left and/or right "congestive" failure is present. In the presence of one or both types of failure the increased venous (i.e., auricular) pressures with increased diastolic volume, enable the work to be maintained. When the venous pressures do not rise, but work of the heart (cardiac output and/or arterial pressures) decreases, "forward" failure is present. Failure thus may be of the left or right "congestive" type, of the "forward" type, of combined left and right "congestive" type, or of "mixed" (congestive and forward) type. In general, the steepness of the slopes of the curves referred to is an expression of the degree of severity of the failure present.

Isolated Heart Preparation.—Aortic pressure fell in only half the cases of "forward" failure, and, in more than half of those in which it fell, the decline in aortic pressure was preceded by a decline in cardiac output; in three experiments both began to fall at the same time. Delayed or absent fall in aortic pressure is due in some to decline in coronary flow with the consequent increase in coronary resistance being sufficient to maintain the total resistance of the two parallel circuits through which the left heart output is distributed. The usual cause, however, for the maintenance of aortic pressure is the existence of a critical level of aortic pressure and cardiac output about which changes of the latter do not appreciably affect the former. This is due to the peculiar relationship of these two in the existent distensible circuit discussed in the text and more fully in a previous report. This fall in arterial pressure is a sign of advanced, rather than early failure. In congestive failure per se, aortic pressure remained constant. Pulmonary pressure relationships are similar to those of aortic pressure, except that coronary resistance increase cannot help maintain pulmonary pressure. In left congestive failure, the equivalent of a gap in the circuit in the isolated heart preparations was responsible for the lack of rise of pulmonary arterial pressure.

With left or right "congestive" failure, left or right venous pressure rose in an accelerating fashion. The development of "forward" failure lessens the rate of rise or even produces a fall, distorting the otherwise exponential type of curve. The venous pressures are increased by the congestion consequent upon decreased power of the heart but are decreased by the lessened load of the heart when the work declines in "forward" failure. Regurgitation due to dilatation of the atrioventricular valve rings in advanced failure may contribute to the rise of venous pressures. Decreased cardiac tonus in failure may lessen this rise.

Coronary flow changes in "congestive" failure, that is, changes in the partition of the cardiac output, occur as in nonfailing hearts. In "forward" failure coronary flow usually decreases when cardiac output falls. Delay or absence of decrease was due, in our experiments, to (1) continuance of spontaneous coronary dilatation present before "forward" failure; (2) increase in peripheral resistance due to adjustment to keep aortic pressure from falling; and (3) increase in peripheral resistance due to decreased distention of the resistance tubing as the aortic-vena cava flow decreases. Thus, no changes in coronary flow occur which are peculiar to heart failure per se.

Calculated work of the heart was found to be similar to cardiac output except when marked "forward" failure was associated with a drop in arterial pressures. However, severe "congestive" failure significantly lessens the true work of the heart since with pressure already high in the blood as it returns to the heart, less work is necessary to raise the pressure to the same degree of arterial pressure. This has been neglected in ordinary calculations of work, which have hitherto ignored initial pressures of the entering blood.

Closed-Circuit Heart-Lung Preparation.—Apart from the fact that in these experiments artificial maintenances of constant cardiac work (when possible) delayed or prevented "forward" failure, changes were essentially similar to those occurring in the isolated heart, except with regard to pulmonary arterial pressure and left venous pressure. Due to the ab-

sence of artificial separation of the pulmonary artery and "pulmonary veins," pulmonary arterial pressure rose in left congestive failure. Moreover, pulmonary edema, when present, caused an accentuated rise in pulmonary arterial pressure and lessened the left venous pressure rise. Both factors lessened the tendency of pulmonary arterial pressure to fall in some cases when "forward" failure developed. In the isolated heart, a similar difference was seen between those experiments in which cardiac output was maintained constant and in those in which it was not.

Effect of Increase in Load.—On several occasions, increasing the cardiac output or artificial resistance initiated or accentuated failure as manifested by the changes in venous pressure. Similarly, in severe failure increasing the blood volume sometimes increased the venous pressures but not the cardiac output, and withdrawing blood sometimes reversed this effect. AUTHORS.

Ricca, R. A., Fink, K., and Warren, S. L.: The Effect of Sulfadiazine, Antitoxins, Globulins, and Dog Plasma on Dogs in Traumatic Shock Under Sodium Pentobarbital Anesthesia. J. Clin. Investigation 24: 146, 1945.

The hazard entailed in giving anesthesia during traumatic shock is not increased by therapeutically effective concentrations of sulfadiazine in the blood stream.

The authors have been unable to detect any beneficial effect of sulfadiazine on traumatic shock, although it does reduce the incidence and amount of gas development from *Clostridium welchii* in the tissues of the traumatized site.

The results on the intravenous administration of 18 Gm. of protein as horse globulin are suggestive that the procedure is beneficial to the clinical course of traumatic shock in dogs under nembutal anesthesia in an environmental temperature of 28° C.

The experiments emphasize the important role that environmental temperature may play in experimental traumatic shock, in determining the survival rate of the animal. They suggest that a study of the effect of therapeutic agents such as gas gangrene antitoxins and plasma should be made at high environmental temperatures (28° C. and above), where the usual survival rate of the traumatized animals is low. AUTHORS.

Katzin, L. I., Ricca, A. R., and Warren, S. L.: Effect of Environmental Temperature and Anesthesia on the Survival of Tourniquet Shock in Rabbits. J. Clin. Investigation 24: 149, 1945.

The temperature of the environment greatly affects survival rates of rabbits on whom tourniquets have been applied for five hours. At 16° C. and below, survival rates are high; at 24° C. and above, survival rates are low. This is in agreement with the findings in crush injury by means of the press in dogs.

Nembutal anesthesia may possibly affect the survival rate since 26 per cent (five out of nineteen rabbits) survived when nembutal was used, and 41 per cent (fifteen out of thirty-six rabbits) survived when no anesthesia was employed in controlled experiments. The room temperature was in the lethal range of 24° C. to 28° C. AUTHORS.

Katzin, L. I., and Warren, S. L.: Thiamine-Deficient Diet in Tourniquet Shock in Rats. J. Clin. Investigation 24: 152, 1945.

In rats, a thiamine-deficient diet for various periods (eleven to thirty-nine days) had no appreciable influence on the survival rate from shock produced by a tourniquet. AUTHORS.

Scholz, D. E., Schultz, J. H., Pleune, F. G., Fink, K., Steadman, L. T., and Warren, S. L.: Study of the Body Temperature and Water Content in Shock Produced by the Continuous Intravenous Injection of Adrenalin, With and Without Anesthesia. J. Clin. Investigation 24: 154, 1945.

Nembutal anesthesia results in a generalized parallel fall in the subcutaneous, intramuscular, and rectal temperatures of the dog.

Injection of adrenalin under the conditions described has no effect on the rectal temperature. The peripheral muscle temperature drop is accentuated.

On the basis of survival time, nembutal anesthesia appears to have a deleterious effect in adrenalin shock.

Applications of heat to the four extremities, in an attempt to raise the peripheral temperatures to normal, did not result in a beneficial effect in adrenalin shock.

In general, the hematocrit was elevated as a result of the injection of adrenalin.

The initial rise in arterial blood pressure when the adrenalin injection is begun is followed by a fall which continues fairly steadily until the animal succumbs.

The most significant finding in the change in percentage of water in the tissues as a result of adrenalin shock was an increase in water content of the heart. Pericardial effusion usually occurs, and edema of the heart was also demonstrated histologically. The quantity of water involved is of no significance to the total water balance.

The findings indicate that, in this type of shock, there is no specific mobilization of water in the tissues which accounts for the rather frequent finding of a rise in hematocrit (hemoconcentration).

Serum potassium and sodium showed no consistent changes. A rather consistent increase (average of 17 per cent) in serum magnesium was found in those dogs given nembutal anesthesia and was attributed to the latter. AUTHORS.

Linton, R. R.: Arterial Embolism. A Simplified Technique for the Removal of a Saddle Embolus at the Bifurcation of the Aorta With a Report of a Successful Case. Surg., Gynec. & Obst. **80**: 509, 1945.

The success of an embolectomy depends on: (1) early operation, (2) direct and adequate exposure of the site of embolism, (3) occlusion of the artery distal to the embolus before the artery is disturbed at, or proximal to, the site of embolism, (4) avoidance of damage to the intima, (5) complete control of the arterial inflow both proximal and distal to the arteriotomy so that (6) a meticulous intima-to-intima closure may be accomplished.

The removal of a saddle embolus at the bifurcation of the aorta is a feasible operation if these principles are followed.

The technique of the operation has been simplified by the use of the tourniquet type of clamp for control of the arteries during the embolectomy.

A saddle embolus at the bifurcation of the aorta may be removed readily through an arteriotomy of the right common iliac artery, with two clamps on this blood vessel and one on the left common iliac artery, without the necessity of freeing up the aorta.

Embolectomy is more readily accomplished by direct exposure of the site of embolism. For this reason a transperitoneal or extraperitoneal approach through a right paramedian incision is recommended for the exposure of the bifurcation of the aorta and the common iliac arteries. AUTHOR.

Naide, M., and Sayen, A.: The Primary Influence of Basal Vascular Tone on the Development of Postocclusive Collateral Circulation and in Selecting Patients for Sympathectomy. Am. J. M. Sc. **209**: 478, 1945.

An objective method is described by which one can predict whether a collateral circulation is likely to develop following a major peripheral arterial occlusion and whether a sympathetic ganglionectomy is indicated. By determining the patient's basal vascular tone, which can be obtained from any unoccluded extremity, it is possible to predict far more accurately the course of the disease and to decide the amount and type of treatment required.

Patients who have a low grade of vascular tone will develop a collateral circulation almost invariably and, as a rule, do not require much treatment. The majority of patients who have a high grade of vascular tone do not develop a collateral circulation; and, since their symptoms are much more severe, require intensive treatment. Only patients with a high grade of vascular tone require sympathetic ganglionectomy.

The previous method for selecting patients for sympathectomy on the basis of their capacity to vasodilate in response to paravertebral or local nerve block is erroneous. The patients who are in most urgent need for sympathectomy are those with high basal vascular tone who do not respond to temporary nerve block. Patients with low vascular tone are not improved by sympathetic ganglionectomy. AUTHORS.

Bain, C. W.: Pericarditis and Complete Heart Block During Thiouracil Therapy. Brit. Heart J. **7**: 49, 1945.

A case of pericarditis with complete heart block is described in a patient receiving methyl thiouracil for thyrotoxicosis. The tonsils were infected, but there was no previous history of rheumatism. AUTHOR.

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